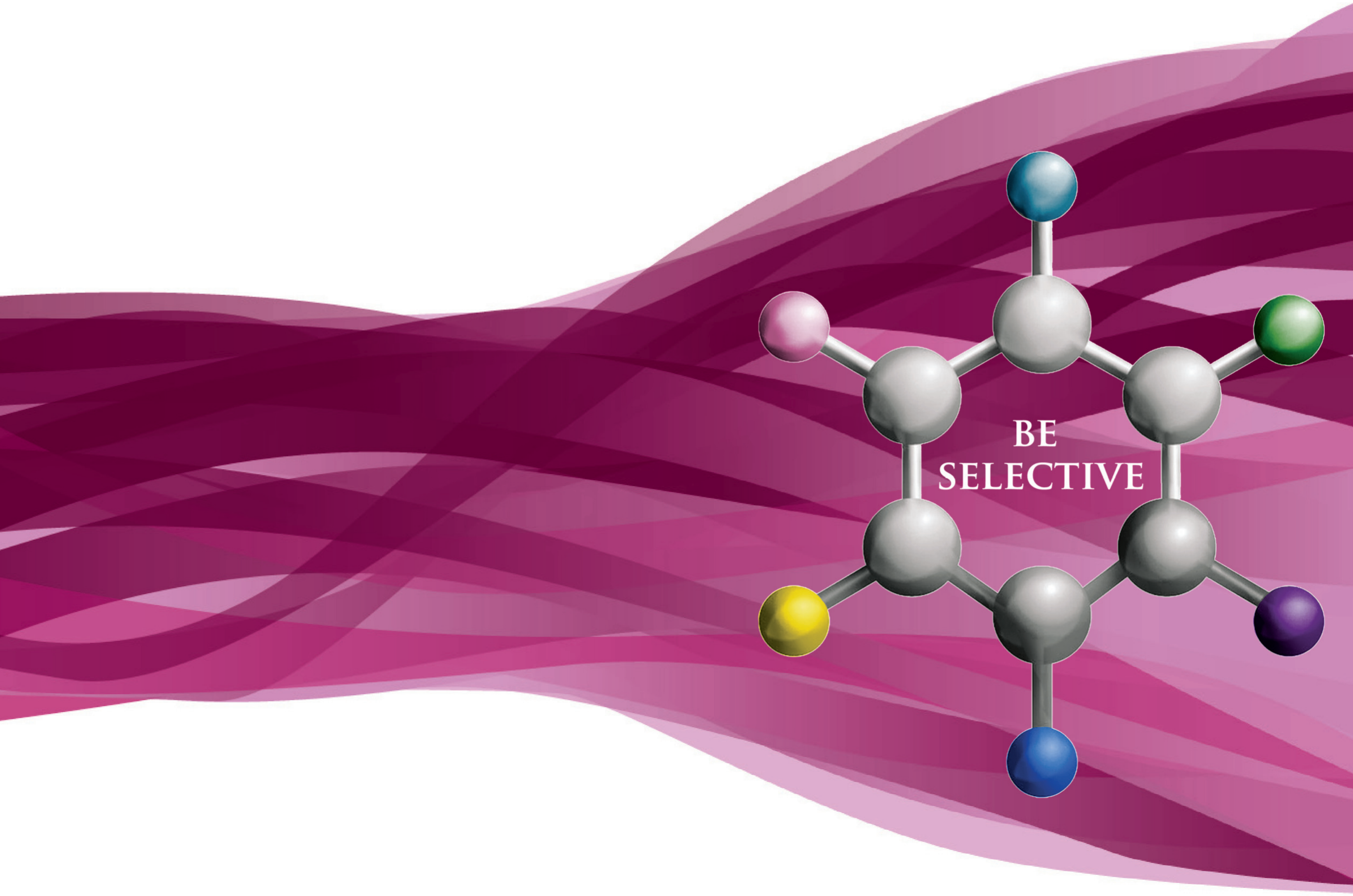
# handbook of pharmaceutical catalysis



Johnson Matthey
Catalysts

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# 1. Introduction

As a recognized world leader in catalysis, Johnson Matthey goes beyond simply providing products and services, working hard to build strategic partnerships with its customers.

With operations in over 30 countries, including dedicated catalyst manufacturing facilities and research centers in the UK, USA, Europe, China and India and customer support teams across the world, Johnson Matthey develops leading edge products and services for the international pharmaceutical and fine chemical sectors.

Our unique platform of experience in base metal, chiral and precious metal catalysts, underpins Johnson Matthey's ability to develop and commercialize catalyst technologies that help our customers succeed.

Whether you are looking for an existing catalyst, customized solution, or hope to improve an existing process, our highly accessible support team is ready to work with you. We are committed to providing our customers with the best technology for optimizing catalytic processes.

This new edition of our technical handbook focuses on the latest catalytic technologies that drive processes in the pharmaceutical and fine chemicals industries.

Enhancements in this version include:

- Expanded Chemistry section in the areas of Coupling, Asymmetric Hydrogenation and Catalytic Deprotection with the most up to date literature references
- Extensive product listings including a new Chiral Homogeneous Catalysts section
- Beneficial reference section containing key factors for optimizing your catalytic process

In addition to continually expanding our broad portfolio of heterogeneous and homogeneous catalysts, enzymes and ligands, Johnson Matthey continues to invest in state-of-the-art equipment for the manufacture, testing, recovery and refining of spent PGM catalysts in order to assist customers with their metal management needs. We also provide catalyst screening services, route design service, process scale-up and optimization services, and custom ligand and catalyst manufacturing services.

The Johnson Matthey name remains synonymous with innovation, accuracy, reliability and integrity. Our global team of experts has the experience to help you choose the best catalyst system for your reaction. Let our catalyst knowledge and experience work for you to improve and optimize your manufacturing processes.

# 2. Catalyst Range

## 2.1 HETEROGENEOUS CATALYSTS

Johnson Matthey offers a full range of heterogeneous catalysts:

- Platinum group metal catalysts (PGM)
- Sponge Metal™ (or skeletal) catalysts
- Other base metal catalysts

### Platinum Group Metal (PGM) Catalysts

### 2.1.1 General Description

Heterogeneous PGM catalysts are in a different phase to the reactants and can be easily separated at the end of the reaction. Examples are:

- catalyst powder (Pd/C) slurried with liquid phase reactants in a batch or continuous process which can be separated by filtration.

- catalyst granules – often called particulates – ($Pt/Al_2O_3$) as a bed through which reactants pass in the gas or liquid phase.

The key properties of a catalyst are:

**High activity:** for fast reaction rate, low catalyst loading and a short reaction time to maximize production throughput.

**High selectivity:** to maximize the yield, eliminate by-products and reduce purification costs.

**High recycle capability:** to minimize process costs.

**Fast filtration rate:** to separate rapidly the catalyst and final product, ensuring maximum production rates.

Heterogeneous catalysts are usually supported on a choice of materials such as activated carbon or alumina to improve metal dispersion, activity and catalyst durability. Supported PGM catalysts are used mainly in hydrogenation, dehydrogenation and selective oxidation reactions. Guidance is provided in Section 4 for the most appropriate catalyst for each specific reaction type. Section 2.1 indicates the most important technical and economic factors that will be of concern to the industrial user of these catalysts.

### 2.1.2 Liquid Phase Reactions with PGM Catalysts

Liquid phase hydrogenations employing heterogeneous catalysts are multiple phase (gas – liquid – solid) systems containing concentration and temperature gradients. In order to obtain a true measure of catalytic performance, heat transfer resistances and mass transfer resistances need to be understood and minimized. Mass transfer effects can alter reaction times, reaction selectivity and product yields. The intrinsic rate of a chemical reaction can be totally obscured when a reaction is mass transport limited.

For a reaction to take place in a multi-phase system, the following steps must occur:

(i) dissolution of gas (e.g. $H_2$) into the liquid phase

(ii) diffusion of dissolved gaseous reactant through the bulk liquid to the catalyst particle

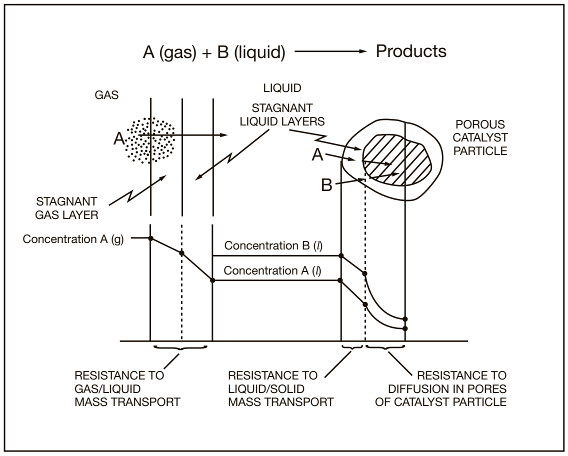
(iii) diffusion of the liquid reactants to the catalyst particle

(iv) in-pore diffusion of the reactants to the catalyst surface

(v) adsorption of reactants on the catalyst, chemical reaction and desorption of products

(vi) diffusion of products from the catalyst pores

**This figure illustrates the three potential mass transfer resistances in a multi-phase catalyst system.**



### Mass Transport

Rates of reaction will be affected by different process variables depending on which step is rate limiting. A reaction controlled by gas–liquid mass transport i.e. the rate of mass transport of the gaseous reactant into the liquid, will be influenced mainly by reactor design, hydrogen pressure and agitation rate.

A reaction controlled by liquid–solid mass transport i.e. the rate of mass transport of either gaseous reactant or substrate from the bulk liquid to the external surface of the catalyst particle, will be influenced mainly by gas or substrate concentration, weight of catalyst in the reactor, agitation and catalyst particle size distribution.

A reaction controlled by pore diffusion–chemical reaction i.e. the rate of reactant diffusion and chemical reaction within the catalyst particle, will be influenced mainly by temperature, reactant concentration, percent metal on the support, number and location of active catalytic sites, catalyst particle size distribution and pore structure. To evaluate and rank catalysts in order of intrinsic catalyst activity, it is necessary to operate under conditions where mass transfer is not rate limiting.

### Reactors

A reactor used for liquid phase hydrogenations should provide for good gas–liquid and liquid–solid mass transport, heat transport and uniform suspension of the solid catalyst.

To facilitate this, a well agitated reactor is essential. The most effective means of agitation at any scale is stirring in a reactor fitted with suitable baffles.

Alternatively, the reactant gas stream may be used to agitate the system and this may be particularly effective when combined with a centrifugal or turbo impeller. Another very effective reactor design is the loop reactor. In this system the reactants are recirculated around a loop by means of a pump and the reaction occurs at the injection nozzle in the reactor. There is very effective gas/liquid/solid mixing at this nozzle.

Many hydrogenation reactions are exothermic and it is necessary to remove the heat of reaction to maintain a constant reaction temperature. This can be achieved with an internal cooling coil or tubes, a cooling jacket or in the case of a loop reactor, an external heat exchanger. A loop reactor system is particularly suitable for highly exothermic reactions.

Continuous liquid phase reactions may be carried out in trickle columns using granular or extrudate catalysts. The reactant, dissolved in a suitable solvent if necessary, is pumped to the column packed with catalyst. The reacting gas, generally hydrogen or oxygen, is passed co-currently or counter-currently through the catalyst bed. The product is collected continuously from the catalyst bed.

### Catalyst Handling and Recovery

Activated carbon-based powder and paste catalysts are both used for liquid phase reactions but paste catalysts, containing approximately 50–60% water within the pores, are preferred when the presence of water in the reaction system is not detrimental. Handling paste, or water wet catalysts, is much easier as it greatly reduces dusting and metal loss. The fire hazard, which occurs when organic vapors are present, is also reduced. When the use of a dry powder is unavoidable, adequate precautions should be taken during handling. (see section 2.1.8.) Ceramic-based catalysts such as those supported on alumina, silica or zeolites, are intrinsically safer and easier to handle because the support is denser than carbon and also is non-combustible. However, different supports may change the catalyst activity.

For maximum economy in the use of PGM catalysts, it is important that the catalyst should be filtered from the reaction system without loss. Various types of leaf, cartridge and centrifuge filters are suitable for this operation, often in conjunction with a polishing filter. The recovery and refining of carbon-based catalyst residues is made easier if any filter precoat that may be required is of a combustible material such as cellulose. Many companies supply equipment suitable for filtering catalysts and Johnson Matthey can provide a list of contacts on request. Johnson Matthey also offers Smopex® metal scavenging fibers. (see section 2.3).

## 2.1.3 Gas Phase Reactions with PGM Catalysts

Granular and pelleted catalysts are used in fixed bed gas phase reactions. The disposition of the catalyst beds, the reactor design and the size and shape of the pellets are dictated by the requirements of the heat transfer, fluid flow and pressure drop in the system. For example, highly exothermic reactions are usually performed in multi-tubular reactors with a coolant fluid surrounding the tubes to remove the heat generated.

Section 4.8 provides detailed information on particulate catalysts and their use.

### Catalyst Charging

Care should be exercised when charging particulate catalysts to fixed bed reactors to minimize physical damage (generation of fines). Note that the catalyst should not fall more than 50–100cm. It should be evenly distributed as the bed is filled and not raked level. One of the best ways to fill a reactor evenly is with a canvas sock connected to an external hopper.

The sock should be kept full and lifted slowly so that the catalyst flows out gently. The sock should be moved around the reactor to distribute the catalyst evenly and not left to discharge into a pile in one position. An alternative method is to fill the reactor with water and slowly add the catalyst such that it sinks gently down through the water.

### Catalyst Activation

Fixed-bed catalysts are sometimes supplied in the unreduced form. These need to be activated before use in the following manner:

(i) Load the catalyst carefully into the reactor and flush away air with flowing nitrogen (or other inert gas) at ambient temperature. (Ensure the volume of nitrogen exceeds 5 x the volume of the reactor)

(ii) Introduce hydrogen at a concentration of 1% into the flowing nitrogen. Check for an exotherm in the catalyst bed. If it does not exceed 20˚C, then slowly increase the temperature (over >60 minutes) to the desired reaction temperature. The low hydrogen concentration will prevent a large exotherm when the catalyst species undergoes reduction.

(iii) Check for any exotherm and gradually increase the hydrogen concentration until 100% hydrogen.

(iv) Slowly introduce the feed to minimize any exotherms until the desired feed rate is achieved.

Note: minimum temperatures of 100˚C for Pd, 120˚C for Ru and 200˚C for Pt catalysts are generally required to ensure complete reduction.

## 2.1.4 Choice of Catalyst Support for PGM Catalysts

Although the main function of the catalyst support is to extend the surface area of the metal, the selection of the best type of support for a particular catalytic metal is important as, in many reactions, the support can also substantially alter the rate and course of the reaction. The type of physical support is largely determined by the nature of the reaction system.

When supported on a high surface area carrier, such as activated carbon, the catalytic metal is present in the form of discrete crystallites (typically a few nanometers in diameter) and these give a very high catalyst area per unit weight of metal.

For liquid phase reactions, powdered supports are invariably used, while in gas phase or continuous liquid phase reactions, a particulate support is used.

The pore structure of the support may modify the role of the metal since the course of a reaction is often greatly influenced by the rates of diffusion of reactants and products within the catalyst pores. In addition, the surface area of a support can limit the PGM concentration that can be usefully employed.

Many of the commonly used catalyst supports, particularly carbon and alumina, are available in a large range of particle sizes, each with a range of surface areas and pore size distributions.

Reaction conditions may limit the choice of support. The support should be stable at the temperature used and should not react with the solvent, feedstock or reaction products.

## 2.1.4.1 Powdered Supports

A good powder catalyst will exhibit high attrition resistance to reduce catalyst losses by fines generation, good suspension characteristics for high catalyst activity and a fast filtration rate to minimize work–up time.

These properties are functions of particle size and shape, pore volume, pore size distribution, surface area, activation procedure and material base.

Values of these parameters may be optimum for one property but less good for another, e.g. a large catalyst particle size will produce a fast filtration rate but poor suspension characteristics.

Thus, Johnson Matthey catalyst supports are selected to incorporate a compromise of properties to generate catalysts of fast filtration with high activity and selectivity.

The following types of powder supports are most commonly used for PGM catalysts:

### Carbon

Activated carbon powder is principally used as a support for catalysts in liquid phase reactions. As carbon is derived from naturally occurring materials there are many variations, each type having its own particular physical properties and chemical composition. These differences can often be related to how the carbon is activated. The two traditional methods in use are steam and chemical activation of the carbon char. In general, chemical-activated carbons tend to have higher BET surface areas than those of steam-activated carbons. By using different activation methods, the surface areas of different carbons can range from 500 $m^2g^{-1}$ to over 1500 $m^2g^{-1}$.

Trace impurities that may be present in certain reaction systems can occasionally poison catalysts. The high absorptive power of carbons used as catalyst supports can enable such impurities to be removed, leading to longer catalyst life and purer products.

Carbon catalysts are produced in two physical forms, dry powder or paste. The latter form contains approximately 50–60% by weight of water which is held within the pores of the carbon. There is no supernatant liquid and the 'paste' catalyst has the consistency of a friable powder.

### Graphite and Carbon Blacks

Graphite powder and carbon blacks have a lower surface area than activated carbon with graphite, generally in the range 5 $m^2g^{-1}$ to 30 $m^2g^{-1}$ (although special high surface area graphites are available in the range 100 $m^2g^{-1}$ to 300 $m^2g^{-1}$). Graphites and carbon blacks are made synthetically and are therefore of higher purity than activated carbons, which are manufactured from naturally-occurring feedstocks. They are used for selective hydrogenation reactions or when a low porosity support is required to minimize mass transfer problems or absorption of high value products.

### Alumina and Other Oxides

Activated alumina powder has a lower surface area than most carbons, usually in the range 75 $m^2g^{-1}$ to 350 $m^2g^{-1}$. It is a more easily characterized and less absorptive material than carbon. It is also non-combustible. Alumina is used instead of carbon when excessive loss of expensive reactants or products by absorption must be prevented. When more than one reaction is possible, a PGM supported on alumina may prove to be more selective than the same metal supported on carbon.

Silica is sometimes used when a support of low absorptive capacity with a neutral, rather than basic or amphoteric character is required. Silica-alumina can be used when an acidic support is needed.

### Calcium Carbonate

Calcium carbonate is particularly suitable as a support for palladium, especially when a selectively poisoned catalyst is required. The surface area of calcium carbonate is low but it finds applications when a support of low absorption or of a basic nature is required. The carbonates of magnesium, strontium and zinc generally offer no advantage over calcium carbonate.

### Barium Sulfate

Barium sulfate is another low surface area catalyst support. This support is a dense material and requires powerful agitation of the reaction system to ensure uniform dispersal of the catalyst. A palladium on barium sulphate catalyst was traditionally used for the conversion of acid chlorides to aldehydes (Rosenmund Reduction) together with an *in situ* partial poison to improve the selectivity. In this application, however, it is being replaced increasingly by palladium on carbon catalysts.

## 2.1.4.2 Particulate Supports

The use of granular or pelleted supports enables catalytic reactions to be carried out continuously in fixed bed reactors. Vapor phase reactions have been carried out in this way, on an industrial scale, for many years.

The advantages of this technique have been extended to liquid phase reactions by the use of trickle-column reactors. Since the formation of fine particles by attrition must be kept to the minimum, high mechanical strength is a basic requirement of these catalysts. Such supports are available in various forms, such as spherical or cylindrical pellets, extrudates or irregular shaped granules.

The metal may be deposited on or near the surface, or it may be uniformly impregnated throughout the support. For most purposes, the diffusion of reactants into the pellet is slow, so that surface impregnation is generally preferred. The quantity of metal that may be deposited on the surface is dependent on the nature of the support. Catalyst life and performance are often affected by the method of preparation.

### Alumina

The most commonly-used pelleted support, alumina, exists in several phases, but the type usually employed is gamma–alumina. The type and form of the alumina support may play a vital role in determining the overall course of the reaction, as may certain ions, which may be deliberately added during catalyst manufacture.

When a support of high mechanical strength is required, or when a much more inert support is necessary, alpha–alumina with a surface area of less than 10 $m^2g^{-1}$ is available.

In some continuous vapor phase processes the catalyst may eventually become deactivated, due to masking of the catalytic sites by the deposition of carbonaceous matter. The catalyst may be regenerated *in situ* by the controlled oxidation of this carbon, taking care to avoid large exotherms in the catalyst bed.

### Carbon

Carbon is usually not strong enough mechanically to withstand the arduous conditions encountered in an industrial gas phase reaction. However, granular carbon is particularly suitable for use as the support in trickle column reactors. Unlike alumina-based catalysts, carbon catalysts cannot be regenerated by a controlled oxidation process.

## 2.1.5 Choice of PGM

Catalyst performance is determined mainly by the PGM component. A metal is chosen based both on its ability to complete the desired reaction and its ability not to perform unwanted side reactions. Palladium is the most versatile of the PGMs. It is typically the preferred metal for the hydrogenation of alkynes, alkenes, carbonyls in aromatic aldehydes and ketones, nitro compounds, reductive alkylations, hydrogenolysis and hydrodehalogenation reactions. Platinum is typically the preferred metal for the selective hydrogenation of halonitroaromatics and reductive alkylations. Rhodium is used for the ring hydrogenation of aromatics, while ruthenium is used for the higher pressure hydrogenation of aromatics and aliphatic carbonyl hydrogenation. The use of mixed-metal catalysts may also provide additional benefits in either selectivity and/or activity by a synergistic effect through the presence of both PGM metals.

## 2.1.6 Choice of PGM Location

Catalyst performance can be altered significantly by the appropriate choice of support material, metal location and dispersion within the pore structure of the support. Johnson Matthey has developed techniques to deposit the metal selectively in the desired location and this is illustrated for a 5% palladium on carbon catalyst in the schematic.

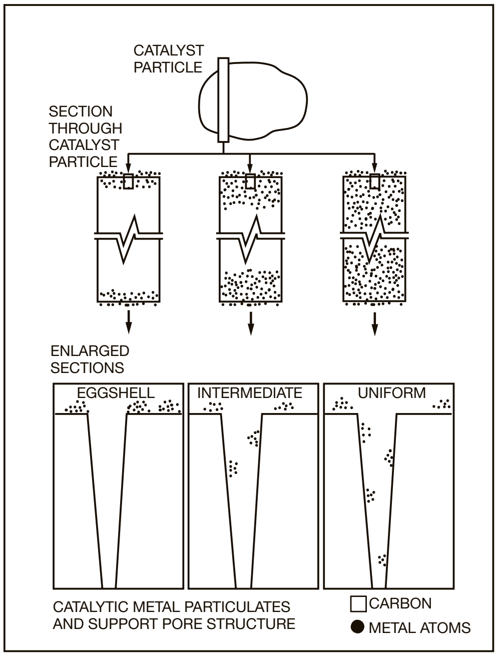
**Eggshell** shows palladium located on the exterior surface.

**Intermediate** shows palladium located deeper within the pore structure.

**Uniform** shows palladium evenly dispersed throughout the support structure.

The catalysts are designed with different metal locations for reactions performed under different conditions of pressure and temperature.

Hydrogenation reactions are generally first order with respect to hydrogen. Thus, the reaction rate is directly proportional to hydrogen pressure. With intermediate and uniform catalyst types, an increasing proportion of the metal becomes accessible as the pressure increases. When all the metal is available, the catalyst properties closely parallel those of an eggshell catalyst. Therefore at higher pressures, intermediate and uniform catalysts have a higher activity than eggshell ones because of their intrinsic greater metal dispersion due to metal located deeper within the support pore structure. Thus, eggshell catalysts would be chosen for high activity at low hydrogen pressure and uniform catalysts at high pressure.



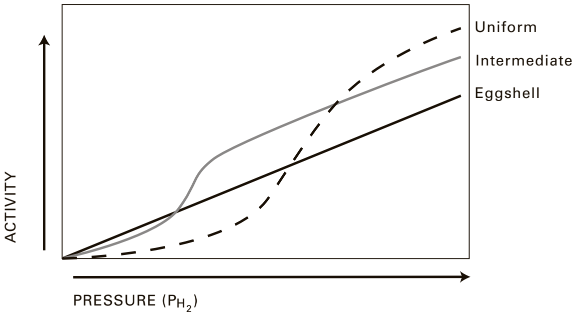
The location of catalytic metal deep into the support may lead to large in–pore diffusion resistance to reactants. This will result in increases in residence time and possible changes in selectivity. Thus the variation of the metal location can be used to adjust the selectivity of the catalyst.

Eggshell catalysts have high activity at low reaction pressures in systems substantially free from catalyst poisons. If a catalyst poison is present, this can be overcome by locating the catalytic metal deeper into the support structure and hence increasing the metal dispersion. Such a catalyst will exhibit greater poison resistance because:

(i) the poison molecules often have high molecular weights and, unlike the smaller reactants, are unable to penetrate the pores where the catalytic metal is located.

(ii) the increased metal area counteracts the constant area of metal rendered inactive by the poison.

**The Effect of Hydrogen Pressure on the Hydrogenation Activity of Catalyst**



Variation of metal location, metal dispersion, metal loading (0.5–10%), catalyst pH and pore structure of the support has enabled the development of a large range of catalysts which are widely used in numerous liquid–phase and vapor–phase industrial processes.

### 2.1.7 PGM Catalyst Deactivation

There are four main mechanisms for catalyst deactivation, namely poisoning, fouling, sintering and physical loss of metal.

Poisoning is caused by the irreversible adsorption of species on the catalyst surface. Such species include heavy metals such as lead, copper and zinc; sulfur-containing species such as hydrogen sulfide and mercaptans; arsenic; amines and carbon monoxide. In general, it is not possible to remove the poisons by a washing or oxidation procedure (an exception is carbon monoxide).

Fouling occurs when the catalyst surface is masked by polymeric materials or tars, and is often referred to as "coking" on fixed-bed particulate catalysts. Fixed-bed (except carbon supported) catalysts can be reactivated by the controlled combustion of the coke using an inert gas stream and/or steam with a low concentration of air. The combustion exotherm should be controlled not to exceed 20˚C. Powder catalysts can sometimes be reactivated by washing with suitable solvents, treating with oxidizing agents to breakdown the polymeric materials to smaller, more soluble species, and reducing to metal.

Sintering occurs when crystallite growth of the catalytic metal decreases the metal surface area. This can arise by thermal sintering, particularly when operating above the Hüttig Temperature (see table below) or by a metal dissolution/re–precipitation mechanism.

Thermal sintering can sometimes cause the collapse of the support pore structure e.g. a phase transition from gamma to alpha-alumina resulting in encapsulation of the metal crystallite. Catalyst deactivation by sintering is usually irreversible.

Catalyst deactivation by physical loss of metal can arise in several ways. Metal may dissolve in the reaction medium and be stripped from the support. Metal may volatilize in high temperature gas phase reactions. The support material may be attacked and start to dissolve in some liquid-phase reactions and the insoluble catalyst fines pass through the filter system. Excessive movement of fixed-bed catalysts due to pressure fluctuations can cause loss of catalyst fines by abrasion. The above forms of catalyst deactivation can be overcome by a more suitable choice of catalyst and/or reaction conditions.

### 2.1.8 Safety and Handling of Supported PGM Catalysts

Platinum group metal (PGM) heterogeneous catalysts are generally non pyrophoric when they are exposed to air in the absence of organic vapors. They can be handled safely on a small scale in the laboratory and pilot plant, and on a large scale in commercial manufacturing. However, they are very effective catalysts for the rapid and exothermic oxidation of combustible organic vapors and compounds. Care must be taken when such catalysts are brought into contact with volatile organic liquids and combustible organic vapors in the presence of air or oxygen. Adherence to some simple precautions can minimize the hazards associated with handling these catalysts. Always refer to the Material Safety Data Sheet (MSDS) for information concerning proper safety and handling, and the use of personal protective equipment.

PGM catalysts can be supplied either water wet or dry. Water wet catalysts typically contain 40 to 70% water by weight. Dry catalysts typically contain 0 to 39% water by weight. Dry catalysts are produced by oven drying water wet catalyst under vacuum at elevated temperatures under an inert atmosphere. The two types require different safety and handling procedures.

Water wet catalysts have water contained in their pore structure and act as free flowing powders. They can be stored and handled in air. They can be safely mixed with most common solvents. Water wet catalysts are used in preference to dry catalysts unless water is incompatible with the reaction system. The safety benefits provided by the water wet catalysts require that the catalyst not be allowed to dry out. Catalyst must be stored in tightly sealed containers as they pose a significant hazard even if only a small portion is allowed to dry out.

**Table: The Hüttig Temperature of the Platinum Group Metals**

| **Metal** | **Pd** | **Pt** | **Rh** | **Ru** | **Ir** | **Os** |
|---|---|---|---|---|---|---|
| **Hüttig Temperature (°C)** | 275 | 340 | 398 | 484 | 542 | 718 |

Care should always be taken when mixing catalysts and organic materials. The risk of spontaneous ignition can be reduced by cooling both the catalyst and the organic material(s) before mixing and performing the mixing operation under a blanket of inert gas, such as nitrogen. Even when using a water wet catalyst, the safest procedure is to add the solvent to the reactor containing the catalyst rather than catalyst to solvent.

Dry PGM catalysts require special handling procedures because the potential for igniting flammable materials is much greater than with water wet catalyst. Dry PGM catalysts, especially platinum and palladium, will ignite low molecular weight solvents such as methanol, ethanol, and isopropanol. Non-combustible solvents should be used whenever possible. The safest solvent is water.

The initial contact of a dry catalyst with a solvent or substrate is preferably completed in an inert atmosphere. As an added precaution, the solvent may be cooled prior to use and should always be added to the catalyst rather than catalyst to the solvent. Once the catalyst is completely wetted with solvent or substrate, it is relatively safe to handle and can be removed from the inert atmosphere. Care must be taken to prevent any of the wet catalyst from drying out. If a non-combustible solvent can be used to wet the catalyst without effecting the reaction, this solvent should be used. Dry catalysts are also capable of causing dust explosions.

After using a catalyst in the presence of hydrogen, the catalyst surface may contain adsorbed hydrogen making the catalyst potentially pyrophoric. Catalyst should be removed from the reaction mixture by filtration under an inert atmosphere. The catalyst should not be allowed to dry out, and should be washed with water and left water wet. It should not come into contact with combustible solvents and vapors. Recovered catalyst should be placed and sealed in an appropriate container keeping the catalyst water wet.

The weighing and handling of catalysts may cause them to lose or gain moisture. The area used to weigh the catalyst should be accessible and free of clutter and sources of potential fuel, such as solvent wash bottles, solvent containers and organic materials. Care should be exercised not to spill any catalyst. Any catalyst, wet or dry, which is spilled should be completely cleaned up using water and kept water wet.

It is recommended that any process using a PGM catalyst have a complete hazard and operability study, and that staff be trained in proper catalyst safety and handling. Use recommended procedures, practice good housekeeping and always think safety first.

### 2.1.9 Packaging and Storage of PGM Catalysts

Johnson Matthey catalysts are normally supplied in polyethylene bags (sealed with plastic clips) which are packed in heavy-duty fiberboard drums. If required, steel or plastic drums can be employed. Also, on request, the catalysts can be packaged in pre–weighed quantities for batch-type processing requirements.

PGM heterogeneous catalyst samples for laboratory evaluation are available packed in glass or plastic bottles.

The catalysts should be stored in their sealed drums to prevent ingress of air and foreign gases until required for use. The drums should be kept in a cool, dry place under reasonable conditions (not exposed to the elements of weather and extremes of temperature – ideally keep between 5 to 30°C). They should not be stored near oils or flammable liquids or exposed to combustible vapors.

After use, the empty bags and drums should be retained for return of the spent supported catalyst.

### 2.1.10 PGM Catalyst Recovery and Shipment

When the catalyst has come to the end of its active life, the spent material can be sent back to Johnson Matthey for recovery of the PGM values. Each batch of residues received is rendered into a form suitable for evaluating the exact metal content.

After use, the filtered supported catalyst should be washed with a suitable solvent, followed by water (to reduce the organics content to a minimum) and returned as damp cake to the bags and drums. These should be sealed and stored away from any combustible vapors.

Since many supported catalysts are more pyrophoric after use in hydrogenation reactions due to hydrogen adsorption, they should ideally be filtered under an inert atmosphere. If this is not possible then the filter cake should not be allowed to ‘dry out’ during filtration, such that air is drawn through the cake before it is washed thoroughly with water (to minimize the organics content) and transferred as a damp cake to the drums for storage.

Other materials contaminated with PGMs, such as wipes, filter cloths or distillation residues should be kept water wet and returned in a separate marked drum for metal reclamation.

Gas-phase pelleted catalysts can usually be returned without any pretreatment for recovery of metal values.

Spent catalyst residues returned to Johnson Matthey are classed as materials for recycling and the transport of these residues is subject to current waste regulations. Johnson Matthey can offer advice about the regulations that apply to different materials, but the classification of any waste material is dependent upon the composition and characteristics of that material and is the responsibility of the originator of the waste.

In addition, all movements of catalyst residues must be classified and labeled according to current transport regulations. To ensure safe treatment of the residues, Johnson Matthey requires a Material Safety Data Sheet for each residue returned.

Further information and assistance on procedures for the return of residues and on the refining service can be obtained by contacting Johnson Matthey. The refining service is described in Section 3.2.

## Base Metal Catalysts

## 2.1.11 General Description and Applications

## PRICAT® Supported Base Metal Catalysts

Johnson Matthey's **PRICAT®** products are supported base metal catalysts for applications in the agrochemical, fine chemical, pharmaceutical intermediate and flavor & fragrance markets. These base metal catalysts are utilized in a vast range of reactions. The varying types and applications include copper based catalysts for dehydrogenation in slurry phase or fixed bed, powdered nickel for miscellaneous hydrogenations and alumina powders for dehydration . The main **PRICAT®** products are kieselguhr and silica supported Ni, Cu and Co catalysts functionalized with dopants. Most of the catalysts in the **PRICAT®** range come in tablet and powdered form. This allows the products to be applied in slurry phase, trickle bed and fixed bed reactors. The powdered catalysts are easy to handle since they are non-pyrophoric, free flowing and have excellent filtration qualities. The **PRICAT®** tablets, used in trickle and fixed-bed applications, usually come in the following sizes:

- 3 x 3 mm
- 5 x 4 mm
- 6 x 5 mm
- 6 x 10 mm

All **PRICAT®** catalysts are reduced and air passivated, allowing for ease of use. In general, activation can be done in situ under mild process conditions and low hydrogen partial pressures. **PRICAT®** catalysts are doped with co-catalytic metals and other additives in order to enhance performance in specific reactions. In addition to the type and loading of additives, the selectivity and activity of the catalyst can be further tuned by altering the support, metal depositioning technique, and reduction and passivation method.

The table below shows some typical compositions and physical appearances of the main catalysts in the **PRICAT®** range. The table shows only the most widely used **PRICAT®** catalysts, and thus does not reflect the full range. Custom catalysts are available on request.

Reactions performed by **PRICAT®**, catalysts include:

- Hydrogenation of sterically-hindered olefins
- Hydrogenation of phenols
- Ammonolysis of alcohols

| **PRICAT** | | | **Metal** | **Support** | **Promotors** | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Powder | Tablet | % | | MgO | $ZrO_2$ | $Cr_2O_3$ | $Al_2O_3$ | MnO |
| NI 52/35 | X | X | 50 | Kieselguhr | X | | X | | |
| NI 55/5 | X | X | 55 | Kieselguhr | X | | | | |
| NI 60/15 | X | X | 60 | Kieselguhr | | X | | X | |
| NI 62/15 | X | | 60 | Kieselguhr | | X | | X | |
| CU 60/8 | | X | 60 | Silica | | | | | |
| CU 60/35 | X | X | 62 | Silica | X | | X | | |
| CO 40/55 | X | X | 40 | Kieselguhr | X | | | | X |

- Selective hydrogenation of phenol to cyclohexanol
- Hydrogenation of mono nitro-aromatics to the amines
- Ring hydrogenation of alkyl-substituted phenols and aromatics
- Hydrogenation of aldehydes, ketones and aldoses to the corresponding alcohols
- Reduction of nitriles to primary and secondary amines
- Selective dehydrogenation of alcohols to the corresponding aldehydes and ketones

# Sponge Metal™ Catalysts

## 2.1.12 General Description

Sponge Metal™ catalysts are used for many of the same heterogeneous chemistries as PGM catalysts. The most common type of reaction are three phase, gas-liquid-solid, reactions. Sponge Metal™ catalysts can be easily separated at the end of the reaction. For slurry phase Sponge Metal™ catalysts, settling, filtration and decantation are common ways to separate the catalyst. Other methods less commonly used in the industry are centrifugation and magnetic separation. (activated Sponge Nickel ™ catalysts are magnetic).

Sponge Metal™ catalysts are prepared from alloys of transition metals and aluminum. The aluminum is leached from the alloy structure, leaving behind an active skeletal metal surface covered in adsorbed hydrogen. The activated catalysts are stored under water to protect them from oxidation. Sponge Metal™ catalysts are in the fully active form when shipped and require no preactivation prior to use.

Sponge Metal™ catalysts are used mainly in hydrogenation, reductive alkylation and dehydrogenation reactions.

## 2.1.13 Sponge Metal™ Liquid Phase Reactions

The principles which govern the use of Sponge Metal™ catalysts are very similar to those described in Section 2.1.1 for heterogeneous PGM catalysts.

### Considerations in the Industrial Use of Catalyst Reactors

Sponge Nickel™ catalysts are most often utilized in slurry-phase, batch, stirred tank reactors. Reactant, solvent (if present) and catalyst are charged to the vessel, air is replaced with an inert gas and the vessel is put under hydrogen pressure. The mixture is mechanically agitated, then heated to reaction temperature. After reaction, the mixture is cooled, agitation stopped and the catalyst allowed to settle. Product can be removed via diptube.

Slurry-phase Sponge Metal™ catalysts are sometimes used in continuous stirred reactors with continuous catalyst separation and recycle. Continuous stirred reactors are beneficial for very fast reactions (e.g.dinitro and dinitrile reductions) prone to by-product formation.

### Sponge Metal™ Catalyst Handling and Recovery

Typically, Sponge Nickel™ catalysts are provided as a powder covered in water (a slurry). The slurry contains approximately 58-60% catalyst solids by weight. Catalyst weight can be accurately determined using displacement. Information on this method can be provided on request.

Activated Sponge Metal™ catalyst is shipped as an aqueous slurry, packaged in steel drums. The material is pyrophoric and classified as hazardous.

Proprietary Johnson Matthey AMCAT® catalysts are activated powdered encapsulated catalysts in which water has been displaced by an aliphatic amine. AMCAT catalysts are in the form of solid $^1/_2$ inch (13mm) cubes that are nonpyrophoric. The active catalyst powder is released after charging into the desired feedstock and/or solvent.

In some reactions, to gain maximum catalyst efficiency, the catalyst is allowed to settle after reaction and the product is decanted off the top using a dip tube. When this is not appropriate, the entire reaction mixture including product, solvent and catalyst can be fed to a filter or other separation device. If the catalyst will remain in the reactor for re-use, it may also be possible to incorporate filters into the reaction vessel to prevent downstream catalyst carryover.
The filtering of Sponge Metal™ catalysts after use is recommended for maximum sustainability. Various types of leaf, cartridge, magnetic and centrifugal filters and separators are suitable for this operation. Downstream polishing filters are often used. If the catalyst settling and product decantation steps are efficient, it may be possible to use only a polishing filter.

### Sponge Metal™ Catalyst Charging

Catalyst can be charged to the reaction vessel by several methods. In the simplest process, the catalyst drum is placed in proximity to the opening of the reactor, the lid is removed and the entire contents are poured into the vessel. Alternately, the slurry is stirred with a shovel or scoop and metered into the vessel. If a drum is overturned into another vessel, it is recommended that a sturdy 2 inch to 4 inch steel grating be placed over the opening to prevent the drum or drum liner from falling into the vessel.

Alternatively, the catalyst drum is emptied into an intermediate mechanically-stirred charge tank. The stirred slurry would then be pumped or educted into the reaction vessel in a separate step. Rather than overturning a drum and pouring catalyst from the drum to a vessel, it is also possible to stir the catalyst mechanically in the drum and then pump or educt the slurry into another vessel.

### Sponge Metal™ Catalyst Activation

Since activated Sponge Metal™ catalysts are already provided in the reduced state, no further pre-activation or pre-reduction treatments are necessary prior to the actual reaction step.

## 2.1.14 Choice of Sponge Metal™ Catalysts

The most common primary base metals formulated into Sponge Metal™ catalysts are nickel, cobalt and copper. Other base metals can be made into Sponge Metal™ catalyst formulations. Sponge Metal™ catalysts often contain other base metal promoters.

Sponge Nickel™ catalysts, used mainly for hydrogenations, are supplied in both unpromoted and promoted forms. The most common promoters are molybdenum (A-7000 series) and iron and chromium (A-4000 series).

Sponge Cobalt™ catalysts find application in selective hydrogenation, e.g. hydrogenation of nitriles to primary amines without the addition of ammonia as selectivity enhancer, or nitro group reduction in the presence of other functional groups such as halide. Sponge Cobalt™ catalysts can also be promoted.

Copper is also incorporated into Sponge Metal™ catalysts as a primary component. Sponge Copper™ catalysts are more commonly used in dehydrogenation rather than reduction chemistries.

## 2.1.15 Choice of Sponge Metal™ Catalyst Particle Size

Sponge Metal™ catalyst performance can be altered significantly by varying the particle size of the grind. The typical standard medium particle size for Sponge Metal™ catalysts is 35 microns, however, other particle sizes are available upon request. Smaller catalyst particle size will, in general, increase catalyst activity but will reduce the ease of catalyst filtration or separation.

## 2.1.16 Sponge Metal™ Catalyst Deactivation

There are four main mechanisms for Sponge Metal™ catalyst deactivation, namely poisoning, fouling, sintering and chemical and physical degradation. Poisoning is caused by the irreversible adsorption of species on the catalyst surface. Such species include heavy metals such as lead, iron or mercury; sulfur containing species such as hydrogen sulfide and mercaptans; arsenic; amines and carbon monoxide. Most poisoning is irreversible, i.e. it is not possible to remove the poisons by washing or other treatment. However, catalyst poisoning by carbon monoxide can be reversible.

Sponge Metal™ active surfaces can be fouled by polymeric materials such as tars or "heavies" . Powder (slurry phase) catalysts can sometimes be partially reactivated by washing with suitable solvents.

Loss of metallic surface area via sintering is more prevalent in copper catalysts than with nickel catalysts. Catalyst deactivation by sintering is irreversible.

Catalyst deactivation by chemical degradation can occur in two ways. The active metal may dissolve in the reaction medium, or the residual aluminum in the catalyst structure can be leached away to the point where the activity decreases unacceptably. Too high a pH will favor leaching of Al, while too low a pH will favor oxidizing conditions and leaching of Ni. It may also be possible for catalysts to mechanically abrade in high-shear reaction systems.

## 2.1.17 Sponge Metal™ Catalysts Safety and Handling

Activated Sponge Metal™ catalysts are all potentially pyrophoric. Fresh catalyst is shipped under a protective layer of water to prevent immediate oxidation by air.

In the event of a splash or spill, immediately flush with water to prevent catalyst drying. Dry catalyst can self-heat and serve as an ignition source for other flammable materials. Contaminated cleaning materials should be disposed of in a safe place where they cannot cause a fire.

Sponge Metal™ catalysts contain adsorbed hydrogen on their surfaces. Depending on the history and storage conditions of the catalyst, small amounts of hydrogen can evolve from the catalyst into the drums. Even though the drums are equipped with a self-venting mechanism, care must be taken when opening containers. No ignition sources should be present in areas where drums are stored, handled and opened.

After use, all catalysts containing absorbed hydrogen may ignite if dried in air, especially in the presence of organic materials. A used, filtered catalyst should therefore be kept water-wet and out of contact with combustible solvents and vapors.

Please refer to the Material Safety Data Sheet for detailed up-to-date information about hazards and safe handling recommendations.

## 2.1.18 Sponge Metal™ Catalysts Packaging and Storage

Sponge Metal™ catalysts are typically supplied in open-head steel drums. For high-purity requirements, custom drums are available with a polyethylene insert. To accommodate customers' particular processes, the catalyst is available in a variety of drum sizes, from 3-gallon (11 litre) to 55-gallon (208 litre). Also, on request, catalysts can be packaged in pre–weighed quantities to match batch size requirements. Sponge Metal™ heterogeneous catalyst samples for laboratory evaluation are available packed in plastic bottles.

Catalyst should always be stored in sealed containers to prevent ingress of air and foreign gases until required for use. Drums should be kept in a cool, dry place under reasonable conditions (not exposed to the elements of weather and extremes of temperature – (ideally keep between 5 to 30°C). Drums should not be stored near oils or flammable liquids or exposed to combustible vapors due to the risk of fire. After use, empty drums can often be retained for shipment of spent catalyst.

## 2.1.19 Sponge Metal™ Catalyst Recovery and Shipment

When the catalyst has come to the end of its active life, Johnson Matthey offers services for reclamation of metal value. Each batch of residues received is rendered into a form suitable for evaluating the exact metal content.

After use, the filtered supported catalyst should be washed with a suitable solvent, followed by water to reduce organics content to a minimum. Spent catalysts should be sealed and stored away from any combustible vapors. Many supported catalysts are more pyrophoric after use in a hydrogenation reaction due to hydrogen absorption. Catalyst filtration should be done under an inert atmosphere and the filter cake should not be allowed to 'dry out'. The filter cake should be washed thoroughly with water.

Other materials contaminated with base metals, such as wipes, filter cloths, distillation residues etc., should be returned in a separate marked drum for metal reclamation.

Spent catalyst residues returned to Johnson Matthey are classed as materials for recycling and the transport of these residues is subject to current waste regulations. Johnson Matthey can offer advice about the regulations that apply to different materials, but the classification of any waste material is dependent upon the composition and characteristics of that material and is the responsibility of the originator of the waste.

In addition to the regulations governing waste shipments, all movements of catalyst residues must be classified and labeled according to current transport regulations.

To ensure safe treatment of the residues and to meet Health and Safety legislation Johnson Matthey requires a Material Safety Data Sheet for each residue returned.

Further information and assistance on the procedures for the return of residues and on the refining service offered can be obtained by contacting your local Johnson Matthey office (see section 9).

## 2.2 HOMOGENEOUS CATALYSTS

### 2.2.1 General Description

In Homogeneous catalysis, the catalyst and all reacting substances are in the same single phase or state of matter. For pharmaceutical and fine chemical applications this is most commonly the liquid phase as a solution of catalyst with all reactants. The actual homogeneous catalyst is generated in solution by the reaction of a stable, well defined coordination compound or organometallic compound ("a catalyst precursor") with other components of the reaction mixture (substrates, acids, bases, etc.). The actual catalyst is formed in trace amounts and is often difficult to detect and identify. The advent of modern analytical techniques has greatly aided in the attempts to identify the illusive true homogeneous catalyst, but more commonly its molecular structure must be inferred from other reaction data.

The study and use of catalyst precursors and homogeneous catalysis has been a major theme in both academic and industrial research since the 1930s but has gained particular prominence since the 1960s. Several Nobel Prizes have been awarded to researchers in the area: Wilkinson and Fischer 1973, Noyori, Sharpless and Knowles 2001 and Grubbs, Schrock and Chauvin 2005. Their work and that of many others has led to a very high level of understanding of mechanisms and catalytic cycles for most of the catalytic chemistries important to the Pharmaceutical and Fine Chemical syntheses.

Several commercial chemical process have been developed using homogeneous catalysis. Examples include DuPont's Ni catalyzed hydrocyanation, Monsanto's Rh catalyzed carbonylation of methanol to acetic acid and Union Carbide's Rh catalyzed low pressure oxo process. Typical areas of homogeneous catalysis involve hydrogenation, oxidation, polymerization, isomerization, cross coupling and metathesis processes.

Johnson Matthey offers one of the largest portfolios of homogeneous catalysts and catalyst precursors for a vast array of applications, some of which are highlighted in this publication. Our continual collaborations with academia and investments in product research and development ensure a continual pipeline of leading edge catalysts technology. Refer to Table 6 for our current offering of products.

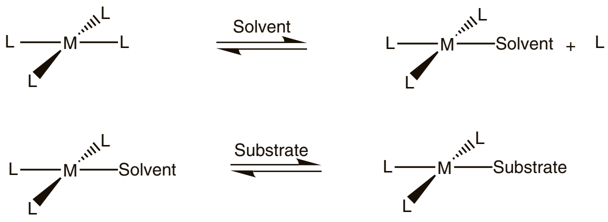
### 2.2.2 Factors Affecting Activity and Selectivity in Homogeneous Catalysis

For molecules to act in a catalytic, as opposed to a stoichiometric mode, the catalyst must be recycled, through a catalytic cycle, whilst reactants are continuously forming the product(s). Two terms are used to measure the activity of a catalyst, the turnover number (TON) is the number of moles of substrate converted to product per mole of catalyst. The second is turnover frequency (TOF $s^{-1}$), this is the number of moles of substrate reacted per unit of time per mole of catalyst.

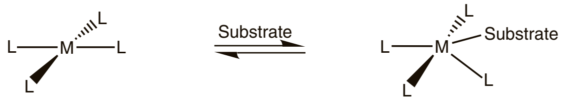
In common with heterogeneous catalysis, the process will affect and alter the homogeneous catalyst. A rate equation for the reaction will contain terms that measure reversible inhibition (by competitive co-ordination) of product, by-products and impurities in the reactants. As the concentration of these materials change during the reaction so the activity of the catalyst will change. In addition, very strong co-ordination can lead to effectively irreversible deactivation of the catalyst. Typical examples of irreversible inhibition of the catalyst are the presence of oxygen in the system and strongly co-ordinating impurities in the substrate. Finally the catalyst itself can be destroyed in the process forming metal particles (metal blacks).

In addition to the activity, a catalyst will also play a significant role in determining the selectivity of the reaction. There are three types of selectivity: *chemo-, regio- and stereoselectivity*. These selectivities are determined by the metal, the co-ordinating groups around the metal and the process conditions (solvent, acid or base additives and temperature). As, in the catalytic cycle, a precise molecular structure including the stereo arrangement of the groups around the metal is important, a highly defined preformed catalyst is preferred when investigating the chemistry. Even after full chemical development of the process a pure pre-formed catalyst often will be superior to the *in situ* system, in terms of activity and selectivity.

The function of the catalyst is to provide a new kinetic route for the reaction – a new route with a lower activation barrier. This route will involve the co-ordination of the reactants at the metal and this will require the metal to have a vacant site(s). To a certain extent this is very similar to adsorption (and desorption) in heterogeneous catalysis. At the most general level the creation of vacant site(s) and coordination of substrate(s) can be envisaged through associative and dissociative pathways. In the *dissociative* pathway the breaking of the metal-ligand bond is usually the rate determining step. During this step a solvent molecule coordinates with the metal and then gives way for the substrate to coordinate. Whereas in the associative pathway, there is a simultaneous making and breaking of the metal-ligand/substrate bonds.



*dissociative pathway*



*associative pathway*

**Figure 1.** Dissociative and associative pathways in homogeneous catalysis.

## 2.2.3 Product Isolation and Full Process Design

The product isolation is typically via crystallization or precipitation. The full process design however needs to consider the fate of the waste materials as they affect process economics and safe and sustainable management of materials. The chemical development of the reaction has optimized and scaled the process to achieve the lowest possible cost of goods. At this stage, a calculation can be made of the cost benefit of recycling any of the components of the waste stream(s). Often solvent recovery is required and distillation facilities are included in the process design. Within this framework the recycle of the metal and safe disposal of co-ordinating ligand can be considered. The usual route would then consist of crystallization of the product, distillation of the mother liquor to recover solvents and then addition of a suitable absorbent to recover the metal and ligand. Activated carbon is the usual choice for the absorbent however Johnson Matthey offers a range of metal scavengers for this application that may provide superior metal recovery (see Smopex section 2.3). The filtered solid waste can be returned to Johnson Matthey for incineration and metal recovery. The ligand is safely incinerated.

The desired product is then further purified by any of the conventional organic chemistry techniques.

## 2.2.4 Homogeneous Catalyst Recovery and Shipment

When the catalyst has come to the end of its active life, the spent material can be sent back to Johnson Matthey for recovery of the platinum group metal values. It is in the catalyst user's interest to concentrate any catalyst containing liquors as much as possible before shipment, thereby:

- reducing freight charges
- reducing residue treatment charges

Spent homogeneous catalyst residues typically contain over 50% organic compounds. Johnson Matthey has considerable experience in handling these types of materials. It is advisable that Johnson Matthey is consulted at the earliest possible opportunity to ensure that the material can be transported with minimum delay. Refining services are described in Section 3.2.

All movement of catalyst residues must be classified and labeled according to current transportation regulations. To ensure safe treatment of the residues and to meet local regulations, Johnson Matthey requires a Material Safety Data Sheet for each residue returned.

## 2.2.5 Homogeneous Catalyst Safety and Handling

It is recommended that any process using a PGM catalyst have a complete hazard operability study, and that staff be trained in proper catalyst safety and handling procedures. Johnson Matthey experts are available to provide advice on the safe use and handlings of its homogeneous catalysts.

# 2.3 SMOPEX®

## 2.3.1 General Description

Smopex® is a metal scavenging system whereby metal binding functionality is externally grafted onto fibres for the recovery of low levels of base and precious metals from solution. Thus allowing fast metal recoveries at high metal loadings and giving vast improvements in process economics.

Smopex® fibres have a unique advantage over traditional polymer beads in that the active groups are located on the surface of the fibre. This enables the efficient recovery of metal from a wide range of process solutions. The fibres are robust and do not degrade while stirring. In addition, they are insoluble in a range of commonly used solvents and are able to be used in both aqueous and organic media.

The main benefits are:

- Smopex® selectively removes ionic and non-ionic metal complexes from aqueous and organic solutions
- Smopex® can be used to remove colloidal precious metal particles from process liquors
- Smopex® can remove metal from both homogeneously and heterogeneously catalyzed reactions
- Smopex® fibres recover metal more quickly and enable a higher loading onto the fibre due to their easily accessible reactive sites. The diffusion rate of the metal is often slower in alternative products
- Smopex® will not break up during stirring
- Smopex® can be used at different pH levels
- Smopex® can be used in all solvents
- Smopex® can recover metal down to ppb levels for discharge to effluent
- A number of Smopex® products can be used in contact with the active pharmaceutical ingredient (API). There is a Drug Master File with the FDA in the USA for use in contact with API

## 2.3.2 Smopex® Application

Precious metal (PM) catalysts have a wide range of applications in fine and bulk chemical manufacturing processes. They provide clean and efficient routes to products in very high yields. The recovery of this metal from process solutions is essential for enabling product purification and improving process economics. For their recovery, traditional techniques such as distillation and precipitation are being superseded by more sophisticated methods, from solvent extraction to ion- or ligand exchange.

For application in the Pharmaceutical and Fine Chemical sectors, Smopex® has been filed with the Food and Drug Administration (FDA) in order that it can be used in pharmaceutical applications for the removal of metal from the product stream containing the Active Pharmaceutical Ingredient (API).
Furthermore, the transportation of certain precious metal containing process materials can be restricted or simply not possible, for a number of reasons:

- Hazardous materials under shipment legislation
- Liquors containing low levels of PMs may not be cost effective to transport and treat
- Material composition confidentiality retention

In these instances, Smopex® can be used at customer sites to remove the metal before shipment, making the shipment possible, non-hazardous, and cost effective.

Smopex® is easily transferable from lab to pilot and plant scale. This flexibility means that its application can be easily tailored to the customer based on their target recoveries, plant requirements, material flow rate and residence times. The three key engineering options below can be improved to meet each customers' individual needs:

- Continuous Column Operation - For continuous, low to medium flows, the column set up can be flexible enough to be situated mid or end of process. Flow can be one pass or recycled.
- Batch Operation - For low, medium and high volume flows, the batch system enables pumping directly to a stirred tank, for treatment with fibre then filtering the fibres off with the metal.
- Johnson Matthey has also patented a filter press plate design to maximize Smopex® effectiveness in high flow applications.

See section 8 for a listing of the available Smopex® products.

# 3. Services

## 3.1 Research Services – Route Design and Chemical Process Development

In addition to our broad portfolio of homogeneous and heterogeneous catalysts, Johnson Matthey offers extensive route design services to support our customers throughout the development, scale-up and commercial implementation stages of a project. We provide comprehensive, cost-effective and time-efficient services for all aspects of chemical process development, implementation and execution. Our aim is to deliver a fully proven chemical process package with chemical engineering parameters (kinetic model, mass transfer resistances) and DOE studies on key process conditions to provide control levels for scale up to full manufacture.

### Partnering with Customers

When providing these services, our goal at Johnson Matthey is to become an extension of our customers' own R&D efforts. We view research projects as opportunities to closely collaborate with customers. Frequent progress reports and direct access to our scientists ensure continual communication throughout the research program and beyond by providing support throughout the duration of the scale-up process.

Projects always begin with preparation of a comprehensive and detailed research plan containing supporting references identified through an extensive chemistry and literature review. Proposals also include a well defined project scope, definitive milestones and clearly established timelines.

### Resources

At Johnson Matthey we have a team of more than 30 scientists with decades of experience in catalysis and organic synthesis working in fully equipped R&D labs located in the UK, US and India. They have access to advanced parallel screening technology, comprehensive analytical instrumentation (NMR, IR, GC, HPLC, LCMS, XPS) and our extensive portfolio of commercially available chemo- and biocatalysts (chiral ligands and catalysts, palladium coupling catalysts, platinum group metal heterogeneous catalysts, Sponge Nickel™ catalysts, alcohol dehydrogenases, esterases). With these resources, Johnson Matthey can provide customers the specialized expertise they need to gain a competitive advantage.

### Capabilities

With our Knowledge Based Screening approach, we can deliver the following services:

- Route development
- Catalyst design
- Catalyst research and selection
- Chemical process development
- Process scale-up

This very flexible range of services covers all stages of the development process. Johnson Matthey can provide gram quantities for feasibility determination, multi-gram quantities for optimization studies and gram to kilogram quantities for the scale-up to commercial production. Our facilities allow us to work with potent molecules including cytotoxics.

Whether you are looking for a specialized catalyst designed specifically for your reaction or assistance with identification of alternative process routes, our team of expert researchers will provide an economical, robust, scalable solution. We work with the earliest drug candidates providing scalable routes for initial tox testing through to launched drugs where cost of goods gives the incentive to find new synthetic routes.

When developing custom-designed catalysts, Johnson Matthey works with the customer to ensure that, from first samples to full plant production, the catalyst meets the desired performance requirements. During the catalyst research program, Johnson Matthey determines the catalyst and reaction conditions most likely to give the desired activity and selectivity, considering only those catalysts suitable for plant scale.

Whether providing a custom catalyst or manufacturing process, Johnson Matthey offers customers and their outsourcing partners global support throughout all stages of development and implementation.

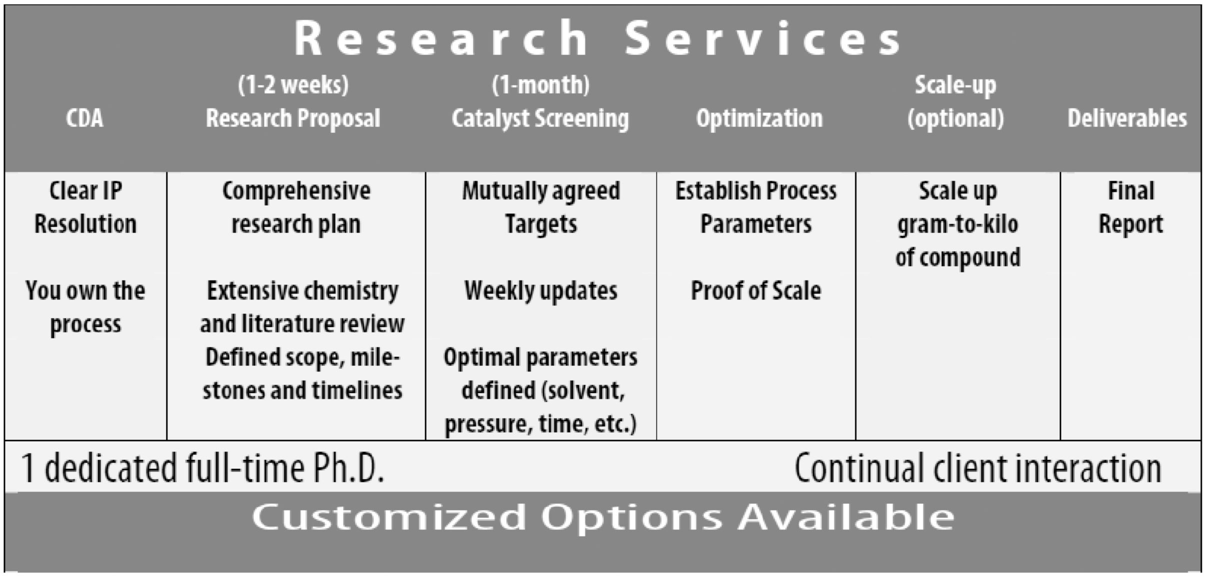
## Project Stages

We also recognize the importance of speed to market. Catalyst research and optimization services are customizable to meet your specific needs.

The chart below describes the various stages of a research project. The customer owns the process from the beginning, with clear confidentiality agreements established early. Preparation of the detailed research proposal takes 1-2 weeks, while catalyst screening typically requires 1 month.

## Customer Commitment

At Johnson Matthey, our overriding commitment is to provide customers with innovative products and services for designing and optimizing synthetic routes. With access to leading edge technology and extensive expertise in catalysts and synthesis, we build optimal solutions for our strategic catalysis partners.



**Research Services**

| CDA | (1-2 weeks) Research Proposal | (1-month) Catalyst Screening | Optimization | Scale-up (optional) | Deliverables |
|---|---|---|---|---|---|
| Clear IP Resolution<br>You own the process | Comprehensive research plan<br>Extensive chemistry and literature review<br>Defined scope, milestones and timelines | Mutually agreed Targets<br>Weekly updates<br>Optimal parameters defined (solvent, pressure, time, etc.) | Establish Process Parameters<br>Proof of Scale | Scale up gram-to-kilo of compound | Final Report |

1 dedicated full-time Ph.D. Continual client interaction

**Customized Options Available**

## 3.2 Refining and Metal Recovery

A key element of the efficiency of metal–catalyzed processes is the recovery of the metal from the process and the refining of the process residues. Johnson Matthey has developed methods for recovering metal from various types of process streams. When a process is in development, Johnson Matthey will evaluate the recovery of the metal from the process and identify a refining route for the residues. This ensures that the process that is put into production is as clean, efficient and cost–effective as possible.

As the largest global full-service refiner of precious metals. our services, technologies and refineries represent the most comprehensive and advanced precious metal refining facilities in the world.

### Traditional Refining

Quotation: From the composition of your residues, Johnson Matthey can identify the best route for the residues in the refinery and quote in advance for all costs.

Shipping: The ways in which the residues of different types of catalyst should be returned are detailed in the appropriate parts of section 2 (see Catalyst Recovery and Shipment). It should be noted that catalyst residues from industrial processes are regarded as waste and are therefore subject to the appropriate waste transport regulations. Johnson Matthey can offer advice on the relevant regulations and the obligations of the consignor.

Receipt: When residues arrive at the refinery, the material is inspected and weighed. This is compared with details advised by the customer. At this stage, the residue is given a unique reference number which is used to identify it at all stages of the evaluation process.

Sampling: All material is rendered to a samplable form. It is weighed, homogenized, and representative samples of the material are taken for analysis.

Analysis: The samples of the material are analyzed in Johnson Matthey's accredited laboratories and the PGM content is accurately established. The results of the analysis are used with the weights to establish the metal content of the material, and the results are reported.

Outturn: At the end of the refining process, the metal outturn is available. It can be:

- transferred to a metal account at Johnson Matthey to provide metal for future catalyst purchases.
- sold, and the proceeds of the sale remitted;
- returned as physical metal;
- or transferred electronically to an account with a third party through Johnson Matthey's world–wide network.

All stages of this process can be witnessed by the customer or the customer's representative, by prior arrangement. Samples are available on request.

### Smopex®

Smopex® is a unique metal 'scavenging' system where chemical groups are attached to fibers, which are then used to attract the required precious and base metal(s).

These functionalized fibers can be placed directly into the process stream to remove the metal* via an ion exchange process. Once recovery is complete, the Smopex® (with the metal attached) can simply be filtered off leaving a pure process liquor behind.

Smopex® fibers are easy to handle and filter. They will not break up during stirring, eliminating particulate contamination and can remove metal from both homogeneously and heterogeneously catalyzed reactions. Smopex® enables the selective recovery of metal from ionic and non-ionic metal complexes from both aqueous and organic solutions.

The use of Smopex® allows recovery from liquors containing low levels of metal even down to parts per billion (ppb) levels.

* Certain Smopex fibres have been filed with the FDA for use in contact with APIs.

# 3.3 Metal Management

Johnson Matthey systems ensure full tracebility and visibility of metal through all stages in the system, from the return of catalyst residues to the re-supply of the metal as catalyst. Metal accounts are available to customers to facilitate the management of metal stocks.

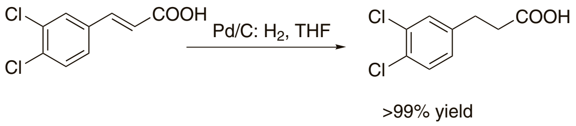
Working closely with our Precious Metals Trading and Marketing unit, we are able to offer you the ability to better manage risk when it comes to sourcing or selling your precious metals. At your request, JM can provide up-to-date market information along with forecasts for future trends. In addition, we can offer procurement alternatives such as spot and forward hedging, and also purchase metal from your refining account. We also offer online services that enable you to view your metal accounts in real time

# 4. Chemistries

## 4.1 HYDROGENATION

### 4.1.1 Carbon–Carbon Multiple Bonds

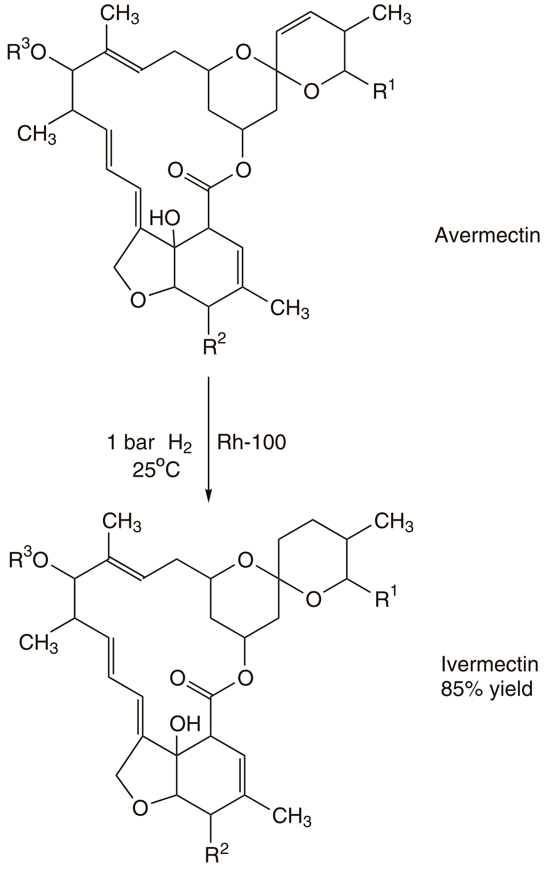
Selective hydrogenation of olefins to the corresponding alkanes are most commonly carried out with either Pd, Pt or Rh catalysts. Palladium catalysts tend to produce a thermodynamically controlled product; Platinum and Rhodium catalysts a kinetically controlled product. Alkenes are hydrogenated to alkanes over supported catalysts with the following general order of activity: Pd > Rh > Pt > Ni >> Ru. The ease of hydrogenation decreases with increasing substitution of the double bond in the order: monosubstituted > 1,1-disubstituted = 1,2-cis disubstituted > 1,2-trans disubstitued > trisubstituted > tetrasubstituted. Product stereochemistry can be affected by the nature of the solvent and the availability of hydrogen to the catalyst. In systems containing multiple double bonds, the least hindered double bond usually reduces preferentially. Exocyclic double bonds are more easily hydrogenated than are endocyclic double bonds.



(1)[1]

A complication in the hydrogenation of alkenes can be double bond migration and cis–trans isomerization. The ability of metal catalysts to promote these reactions is generally in the order: Pd > Ni > Rh > Ru > Pt = Ir. Platinum catalysts are therefore useful when double bond migration is to be avoided.

Homogeneous Rh and Ir catalysts can be particularly useful for selective alkene hydrogenations. For example, in the manufacture of the pharmaceutical Ivermectin, only one of several carbon-carbon double bonds is hydrogenated in the presence of Wilkinson's catalyst, Rh-100 $RhCl(PPh_3)_3$. Rh-100 is normally selective for hydrogenation of the least substituted double bond. Arene, carboxylic acid, ester, amide, nitrile, ether, chloro, hydroxy, nitro and sulfur groups are all tolerated. Catalysts such as Ir-90 $[Ir(COD)(py)PCy_3]PF_6$, Ir-93 $[IrCl(COD)]_2$, Rh-93 $[RhCl(COD)]_2$ or Rh-97 $[Rh(nbd)_2]BF_4$ are used for hydrogenating highly substituted double bonds. Asymmetric hydrogenations are possible using chiral ligands (See Asymmetric Hydrogenation section 4.9.1).



Alkynes can be readily hydrogenated to alkenes or alkanes under mild conditions using Pt or Pd supported catalysts. The catalytic hydrogenation of alkynes generally is more facile than that of any other functional group. Terminal acetylenes are most easily reduced. The selective hydrogenation of an alkyne to an alkene without further hydrogenation to the corresponding alkane can be carried out with a Pd or Ni catalyst. Palladium catalysts are most often used with the addition of a variety of modifiers to improve reaction selectivity. Modifiers include Pb, Cu or Zn metal salts, amines, sulfur-containing compounds and hydroxides. The best known and most commonly used catalyst of this type is Lindlar's catalyst; a Pd catalyst on a calcium carbonate support modified by the addition of lead acetate. Selectivity to the alkene can also be improved by limiting the hydrogen availability. In the absence of isomerization, the selective hydrogenation of a disubstituted alkyne will produce the cis alkene.

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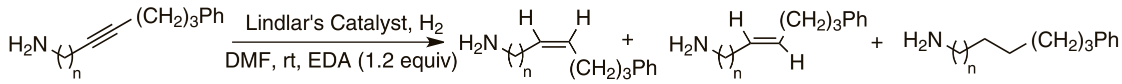
[1] Blaser, H.-U.; Indolese, A.; Schneyder, A.; Steiner, H.; Studer, M. *J. Molec. Catal. A: Chemical* **2001**, *173*, 3.



(2)[2]

> 90% selectivity

| Reaction | Temperature (°C) | Pressure (bar) | Solvent | Catalyst | Catalyst Recommendation |
|---|---|---|---|---|---|
| -C≡C- → -$CH_2CH_2$- | 50-100 | 1–10 | None or alcohols | Pd/C | A405028-5, A503023-5, A102023-5, 5R434, 5R393 5R87L |
| -C≡C- → -CH=CH- | 5–50 | 1–3 | Alcohols, acetic acid, ethyl acetate or vapor phase | Pd/C | A102038-5 |
| | | | | Ni | A-5000 |
| | | | | Ni/Mo | A7063 |
| | | | | Pd(S)/C | A103038-5 |
| | | | | Pd/$CaCO_3$ | A303060-5<br>5R405 |
| | | | | Pd,Pb/$CaCO_3$ | A305060-5<br>A306060-5 |
| -CH=CH- → -$CH_2CH_2$- | 5–100 | 3–10 | None, alcohols, acetic acid or ethyl acetate | Pd/C | A405028-5, A102023-5, A503023-5, A503038-5, 5R434, 5R393, 5R87L |
| | | | | Pt/C | B103032-5, B501032-5, 5R128M, 5R103 |
| Selective hydrogenation of least substituted alkene | 25–75 | 1–5 | Methanol, ethanol, acetone, THF or toluene | Rh | 100 |
| Hydrogenation of substituted double bonds | 25–75 | 1–5 | Dichloromethane, toluene or ethanol | Ir<br>Rh | 90, 93<br>93, 97 |

## 4.1.2 Aromatic Ring Compounds

### Carbocycles

The catalytic hydrogenation of substituted benzenes is used to produce substituted cyclohexanes. The activity of catalysts for the hydrogenation of aromatic rings are in the order Rh > Ru > Pt > Ni > Pd. The rate of hydrogenation of the aromatic ring varies with the nature and position of any substituents. The presence of amine or hydroxyl groups generally has little effect on the reaction. Typical operating conditions for heterogeneous Rh catalysts are 20 to 60ºC and 15 to 60 psi $H_2$ pressure. Higher reaction temperatures and pressures are required for the other catalytic metals. The performance of Ru catalysts can often be improved by the addition of small amounts of water. Product stereochemistry depends on the catalyst used and the nature of any ring substituents. Cis products, where all hydrogen atoms are added to the same side of the chemisorbed ring, are generally formed. In general, homogeneous catalysts offer no advantage and are rarely used for ring hydrogenations.

For the hydrogenation of alkyl-substituted polycyclic aromatics Rh and Pt catalysts are generally less selective than Ru unless the aromatic ring is highly substituted. Partial hydrogenation of benzene to cyclohexene can be affected at 25–200°C and 10–70 bar with a heterogeneous Ru catalyst. Ru is often recommended if C–O or C–N bond hydrogenolysis is to be avoided. In general, hydrogenolysis during ring reduction is decreased with increased pressure and lower reaction temperature. Basic additives may also be used to suppress unwanted hydrogenolysis or coupling reactions and to increase the hydrogenation rate. There is considerable interest in the ring hydrogenation of 4-t-butylphenol to the *cis*-isomer (as opposed to the *trans*

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2 Campos, K. R.; Cai, D.; Journet, M.; Kowal, J.J.; Larsen, R.D.; Reider, P.J. *J. Org. Chem.* **2001**, *66*, 3634.

| Reaction | Temperature (°C) | Pressure (bar) | Solvent | Catalyst | Catalyst Recommendation |
|---|---|---|---|---|---|
| Carbocyclic ring | 5–150 | 3–50 | None or alcohols | Rh/C | C101023-5,C101038-5, 5R20A, 5R594 |
| | | | | $Rh/Al_2O_3$ | C301011-5, 5R524 |
| | | | | Ru/C | D101023-5, D101002-5, 5R97, 5R619 |
| | | | | Pt/C | B103032-5, B501032-5, 5R128M, 5R103 |
| | | | | Pd/C | A503023-5, A102023-5, A102038-5, 5R39, 5R338M, 5R87L |
| | | | | Ni | A-5000 |
| Phenol →Cyclohexanone | 30–200 | 1–10 | None | Pd/C | A102023-5, A105023-5, 5R487, 5R369 |

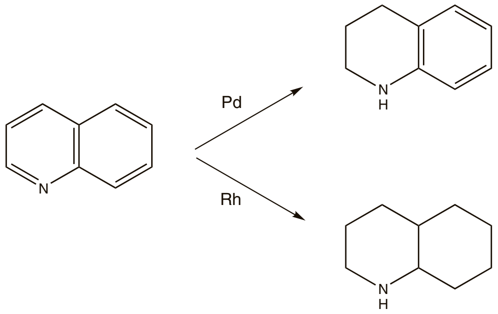
isomer). Choice of a specific Rh on carbon catalyst together with the use of a non-polar solvent (e.g. hexane) can yield >90% of the desired *cis*-isomer. Increased solvent polarity (e.g. isopropanol) results in the production of increasing quantities of the *trans* product.

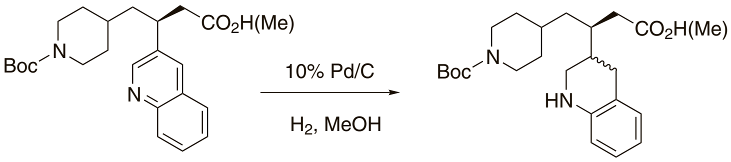
In summary, selectivity is affected by:
- choice of catalyst (including bimetallics)
- solvent polarity and pH
- reaction conditions (temperature and pressure).

Phenols can be converted directly to cyclohexanones under basic conditions using Pd catalysts. Basic alkali or alkaline earth metal ion modifiers are required for selectivity. Liquid phase reactions are typically run with reaction temperatures and pressures between 50 – 180°C under 5 – 15 atmospheres of $H_2$ with a sodium or calcium, hydroxide or carbonate, modifier.

## Heterocycles

In general, heterocycles are easier to hydrogenate than carbocycles. Heterocyclic compounds such as pyridines, quinolines, isoquinolines, pyrroles, indoles, acridines and carbazoles can be hydrogenated over Pd, Pt, Rh and Ru catalysts. Acidic solvents such as acetic acid and aqueous HCl are often used to facilitate hydrogenation as the pyridinium salt is more easily reduced than is the free base. Typical operating conditions for heterogeneous Pt catalysts are 25 to 40°C and 50 to 70 psi $H_2$ pressure. Other catalytic metals are generally less effective than Pt and require higher reaction temperatures and pressures. Rhodium catalysts can be susceptible to poisoning by the piperidine product. Rhodium can also be an active catalyst under mild conditions and is recommended when hydrogenolysis is to be avoided. Palladium is an effective catalyst especially for the hydrogenation of acyl- or acyloxy- pyridines. Generally, Pd is the preferred catalyst for selective hydrogenation of nitrogen-containing heterocyclic rings in the presence of carbocylic rings





(1)[1]

Ruthenium is an excellent catalyst at elevated temperatures and pressures where N–dealkylation or deamination is to be avoided. Hydrogenation of furans and other oxygen-containing heterocycles becomes more complex due to the possibility of hydrogenolysis and ring cleavage reactions. Hydrogenolysis is generally promoted by high temperature and acidic solvents.

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[1] Zhang, F.-Y.; Pai, C.-C.; Chan, A. S.C. *J. Am. Chem. Soc.* **1998**, *120*, 5808.

| Reaction | Temperature (°C) | Pressure (bar) | Solvent | Catalyst | Catalyst Recommendation |
|---|---|---|---|---|---|
| Pyridines | 30-150 | 3-50 | None or alcohols | Pt/C | B102022-5, B103032-5, B501032-5, 5R117, 5R128M, 5R18MA |
| | | | | Ni | A-5000 |
| | | | | Rh/C | C101023-5, C101038-5, 5R20A, 5R594 |
| Furans | 30-100 | 5-60 | None, alcohol or water | Pd/C | A503023-5, A102023-5, A102038-5, 5R434, 5R338M, 5R487 |
| | | | | Rh/C | C101023-5, C101038-5, 5R20A, 5R394 |
| | | | | Ru/C | D101023-5, D101002-5, 5R97, 5R619 |
| Pyrroles | 30-100 | 3-50 | Acetic acid or alcohol/acid | Pd/C | A503023-5, A102023-5, 5R434, 5R87L, 5R39 |
| | | | | Pt/C | B101022-5, B103032-5, B501032-5, 5R117, 5R128M, 5R18MA |
| | | | | Rh/C | C101023-5, C101038-5, 5R20A, 5R594 |

## 4.1.3 Carbonyl Compounds

### Aldehydes

In general, saturated aliphatic aldehydes can be hydrogenated over Pt, Ru, Sponge Nickel™ or Ir catalysts to the corresponding primary alcohols at 5–150°C and 1–30 bar hydrogen pressure. Pd tends to be an ineffective catalyst for aliphatic aldehydes but is the metal of choice for aromatic aldehydes. Ru is the catalytic metal of choice for the hydrogenation of aliphatic aldehydes. A surface layer of oxide generally covers Ru catalysts and this layer must be reduced before the catalyst becomes active. Hence, when using Ru catalysts one will often observe an induction period before the chemistry starts. This can be avoided by pre-reducing the catalyst in-situ in the reaction solvent at > 80°C for 1 hour before introducing the substrate. Hydrogenations using Ru have often shown enhanced kinetics when carried out in the presence of water.

Often when Pt is used as the catalytic metal, the reaction will slow and cease prior to completion. Flushing the reactor with nitrogen and then air before re-purging and pressurizing with hydrogen can usually restart the reaction. This air exposure of the catalyst is thought to remove contaminant built-up on the catalyst surface, in particular carbon monoxide gas. Perhaps a more desirable way to avoid this deactivation is to incorporate a small amount of Sn(II) or Fe(III) chlorides in the reaction mix (0.1 mmol).

A well-known example of aldehyde hydrogenation is the transformation of glucose to sorbitol in aqueous solution. This reaction is traditionally performed industrially with a Ni catalyst, but there are advantages to be gained by using a Ru catalyst.

These are:

- lower operating temperatures, hence better selectivity to the product
- lower operating pressures, hence more general availability of plant
- unlike Ni, Ru is not leached into the sugar solution so this particular product purification step/ environmental hazard is eliminated

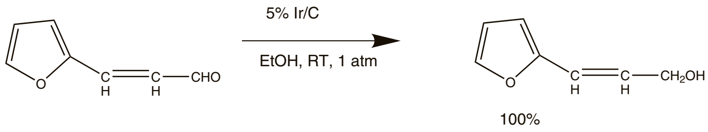
Ether formation can also be reduced using a Ru catalyst.

In the hydrogenation of aromatic aldehydes, Pd is the preferred catalytic metal. Typical reaction conditions are 5–100°C and 1–10 bar hydrogen pressure. Pd will also catalyze the production of hydrocarbon formed from the hydrogenolysis of the alcohol intermediate. Acidic conditions and polar solvents promote the formation of the hydrocarbon by-product.

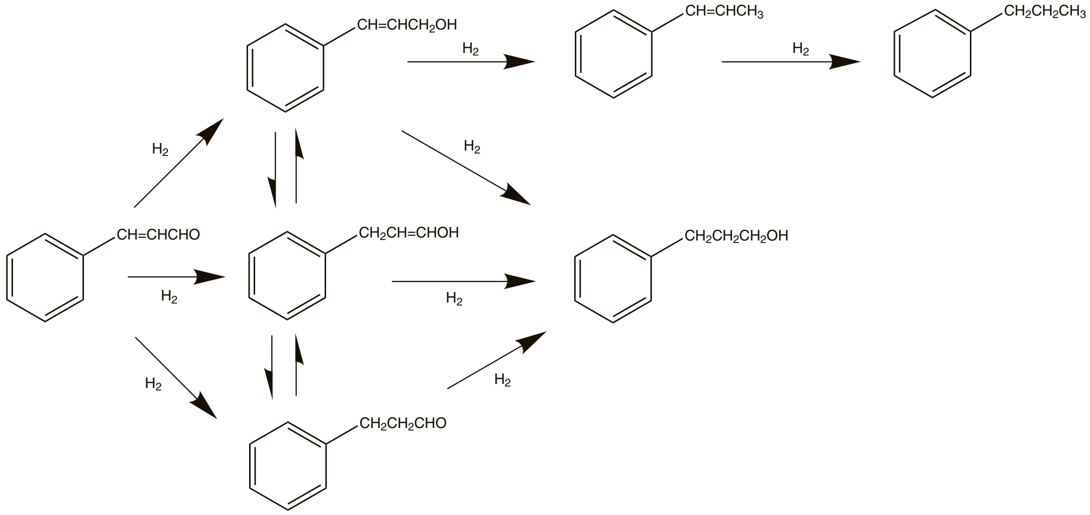
Although Pt and Ru can be considered for this application, there is the possibility of simultaneous ring hydrogenation. To some extent, this side reaction can be inhibited by the addition of either salts of Zn, Ag or Fe (typically <1 mol % with respect to the catalytic PGM) or low molecular weight aliphatic nitriles. In the special case of haloaromatic aldehydes to the corresponding haloaromatic alcohols, Pt is the metal of choice. Extensive hydrodehalogenation will occur with Pd catalysts.

Of particular interest is the selective reduction of α–β unsaturated aldehydes such as crotonaldehyde and especially cinnamaldehyde. A generalized reaction scheme is shown below. Carbonyl hydrogenation is generally less facile than olefin hydrogenation thus making selective reduction of the α–β unsaturated aldehyde to the α–β unsaturated alcohol quite difficult.

Pt/C or preferably Pt/graphite is used commercially to produce cinnamyl alcohol from cinnamaldehyde. The selectivity to the desired product is enhanced by the addition of small amounts of zinc acetate (to inhibit the C=C bond hydrogenation) and ferrous chloride (to enhance the C=O hydrogenation) to the reaction mix. Os and Ir catalysts have also been shown to be highly selective for the formation of α-β unsaturated alcohols e.g. acrolein, crotonaldehyde and cinnamaldehyde.



Cinnamyl alcohol has also been produced in the laboratory from cinnamaldehyde using water-soluble Ru and Ir homogeneous catalysts. Pd/C is used to produce dihydrocinnamaldehyde. Dihydrocinnamyl alcohol is the product when both reducible functions are hydrogenated.



| Reaction | Temperature (°C) | Pressure (bar) | Solvent | Catalyst | Catalyst Recommendation |
|---|---|---|---|---|---|
| ***from Aldehydes***<br>to aliphatic alcohols | 5-150 | 1-10 | Alcohols, ethyl acetate or water | Ru/C | D101023-5, D101002-5, 5R97, 5R619 |
| | | | | Pt/C | B103032-5, B103018-5, B501032-5, 5R128M 5R103 |
| to aromatic alcohols | 5-100 | 1-10 | Neutral: benzene, hexane, DMF or ethyl acetate | Pd/C | A503023-5, A102023-5, A570129-5, 5R374, 5R487, 5R87L |
| RR'C=O → RR'$CH_2$ | 5-100 | 1-10 | Acidic: alcohol or acetic acid | Pd/C | A503023-5, A503038-5, A102023-5, 5R37, 5R39, 5R393 |
| Glucose → Sorbitol | 100-120 | 20-30 | Water | Ru/C | D101023-5, D101002-5, 5R97, 5R619 |
| α-β unsaturated aldehyde to unsaturated alcohol | 50-120 | 5-15 | Isopropanol | Pt/C | B103032-5, B103018-5, B501032-5 |
| | | | | Pt/Graphite | 5R289 |
| | | | | Ir/Graphite | 5R728 |

## Ketones

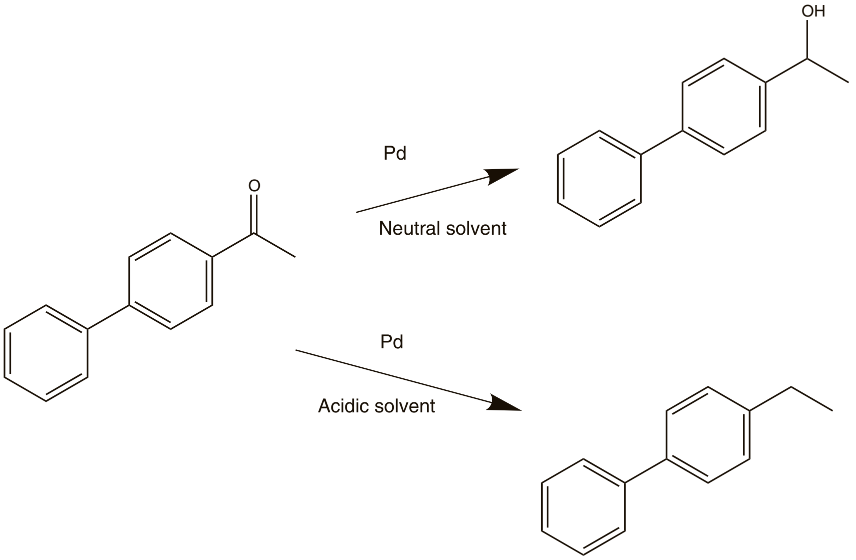
Ketone hydrogenation is similar to that of aldehyde hydrogenation, but is usually less facile due to increased steric hindrance and lower electrophilicity at the carbonyl group. Saturated aliphatic ketones can be hydrogenated over Pt, Ru or Ir to the corresponding secondary alcohol at 5–150°C and 1–30 bar hydrogen pressure. Ru is the catalytic metal of choice for the hydrogenation of water-soluble ketones and for hydrogenations in alcohol solvents (since ether formation is minimized).

Aromatic ketones are best hydrogenated over Pd catalysts and can be hydrogenated to the corresponding alcohol or alkyl aromatic (by hydrogenolysis). Acidic conditions, elevated temperatures and polar solvents favor hydrogenolysis.

The selective hydrogenation of an $\alpha$-$\beta$ unsaturated ketone to the corresponding $\alpha$-$\beta$ unsaturated alcohol is much more difficult than is the case for the $\alpha$-$\beta$ unsaturated aldehydes. However, if the alkene is particularly sterically crowded then some success may be achieved for example using Sponge Cobalt™. Hydrogenation of the $\alpha$-$\beta$ unsaturated ketone to the saturated ketone is relatively trivial with a Pd catalyst as would be expected.

Ketones can be hydrogenated to alcohols using homogeneous catalysts such as Ru–100. The reaction is promoted by base. Homogeneous catalysts are particularly attractive for performing enantioselective hydrogenations on functionalized ketones.

Please see section 4.9.2 for information on asymmetric ketone reduction.



| Reaction | Temperature (°C) | Pressure (bar) | Solvent | Catalyst | Catalyst Recommendation |
|---|---|---|---|---|---|
| ***from Ketones*** | | | | | |
| to aliphatic alcohols | 5-150 | 1-10 | Alcohols, ethyl acetate or water | Ru/C | D101023-5, D101038-5, D101002-5. 5R97, 5R600, 5R619 |
| | | | | Pt/C | B103032-5, B103018-5 B501032-5, 5R128M, 5R103 |
| to alcohols | 15-100 | 1-50 | Toluene, THF, methanol, ethanol or propan-2-ol | Ru | 100 |
| to aromatic alcohols | 5-100 | 1-10 | Neutral: benzene, hexane, DMF or ethyl acetate | Pd/C | A503023-5, A102023-5, 5R87L, 5R434, 5R374 |
| RR'C=O → $RR'CH_2$ | 5-100 | 1-10 | Acidic: alcohol or acetic acid | Pd/C | A503023-5, A503038-5, A102023-5, 5R39, 5R434, 10R39 |

## 4.1.4 Nitro and Nitroso Compounds

Aromatic nitro compounds are hydrogenated to the corresponding amine over Pd, Pt and Sponge Metal$^{TM}$ catalysts. An aromatic nitro group is generally the most easily hydrogenated of all functional groups and proceeds under very mild conditions. Nitro functions are reduced so readily that hydrogen mass transfer effects and resistances may influence the overall reaction rate. The analogous aliphatic compounds are less easily hydrogenated as the resulting amine has more of a tendency to inhibit the catalyst. Higher catalyst loadings and more vigorous reaction conditions are sometimes required. To some extent this inhibiting effect can be decreased by operating under acidic conditions. Nitro and nitroso hydrogenations are usually performed using heterogeneous catalysts. Intermediate hydroxylamines, oximes and azo- compounds can be obtained depending upon the reaction conditions employed.

Aromatic nitrobenzenes can be converted to p-aminophenols using catalytic hydrogenation. The reaction is typically run in dilute sulfuric acid using a Pt/C catalyst and a phase transfer catalyst (i.e. a water soluble quaternary ammonium compound) under carefully controlled reaction conditions.[1]

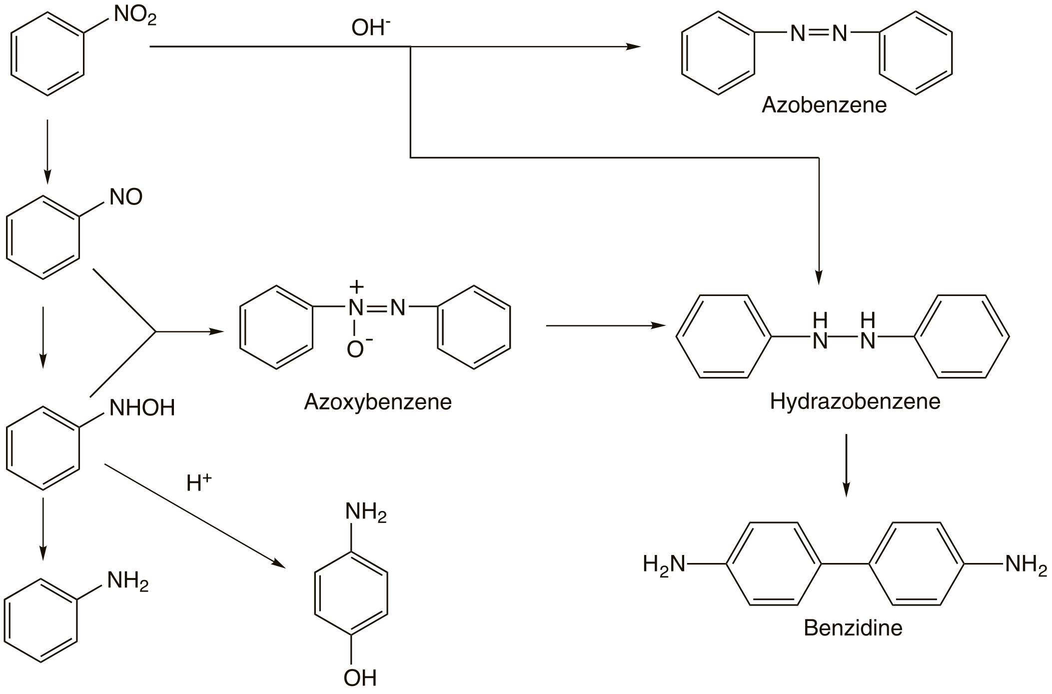
Solubility of platinum group metals from heterogeneous catalysts during hydrogenation has long been a problem, particularly during the reduction of nitroaromatics to aromatic amines. Reaction hydrogen mass transfer limitations can result in the dissolution of supported metals into the reaction solution. This problem can be minimized by ensuring that the rate of hydrogen arrival at the catalyst metal surface is greater than the rate of consumption; i.e., by reducing or eliminating hydrogen mass transport limitations.[2]

The hydrogenation of nitro compounds is a very exothermic reaction:

$$RNO_2 + 3H_2 \rightarrow RNH_2 + 2H_2O \quad \Delta H = -431 \text{ kJ/mole}$$

It is therefore desirable to use a solvent as a heat sink.

**Reaction pathways for the hydrogenation of the nitro group**



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[1] Tanielyan, S.K.; Nair, J.J.; Marin, N.; Alvez, G.; McNair, R.J.; Wang, D.; Augustine, R.L. *Org, Process Res. Dev.* **2007**, *11, 681.*
[2] Bird, A. J.; Thompson, T. *Catalysis in Organic Syntheses* **1980**, 61.

| Reaction | Temperature (°C) | Pressure (bar) | Solvent | Catalyst | Catalyst Recommendation |
|---|---|---|---|---|---|
| ***From Nitro Compounds*** | | | | | |
| to aromatic amine | 5-50 | 1-5 | Neutral or acidic alcohols, ethyl acetate | Pd/C | A401102-5, A405028-5, A503023-5, A503032-5, A102023-5, 5R37, 5R434, 5R87L, 5R315, 5R393 |
| | | | | Ni | A-5000 |
| | | | | Pt/C | B103032-5, B501032-5, 5R18, 5R128M, 5R103 |
| to aliphatic amine | 50-150 | 3-25 | Alcohols<br>Base causes inhibition. Acid sometimes improves activity | Pd/C | A401102-5, A405028-5, A503023-5, A503032-5, A102023-5, 5R395, 5R434, 5R87L, 5R58 |
| | | | | Ni/Mo | A-7000, A-7063 |
| | | | | Pt/C | B103032-5, B501032-5, 5R128M, 5R117, 5R103 |
| | | | | Rh/C | C101023-5, 5R20A |
| to haloamines | 5-50 | 1-5 | Alcohols, ethyl acetate | Pt/C | B101032-3, B103032-3, B102032-1, B101038-1, B105047-1, 1R18MA, 3R128M, 1R128M, 1R117 |
| to p-aminophenols | 50-150 | < 1 | Dilute $H_2SO_4$ | Pt/C | B102032-1, B105047-1, 1R199 |
| ***From Nitroso Compounds*** | | | | | |
| to aromatic amine | 5-100 | 1-10 | Neutral or acidic alcohols, ethyl acetate | Pd/C | A503023-5, A503032-5 A505085-5, A102023-5 5R434, 5R338M, 5R87L |
| | | | | Pt/C | B103032-5, B501032-5 5R128M, 5R103 |
| to aliphatic amine | 5-100 | 1-10 | Alcohol/HCl or acetic acid | Pd/C | A503023-5, A503032-5, A505085-5, A102023-5 5R434, 5R338M, 5R87L |
| | | | | Pt/C | B103032-5, B501032-5, 5R128M, 5R103 |

**Note:** Many processes are operated commercially without solvent, using molten substrate at temperatures higher than those indicated above

## 4.1.5 Halonitroaromatics

Selective hydrogenation of halonitroaromatics to the corresponding haloaminoaromatics are most commonly carried out with Pt catalysts. Palladium catalysts generally cause high levels of dehalogenation. The extent of dehalogenation depends on the halogen (I > Br > Cl > F), and its position on the aromatic ring with respect to the nitro group being hydrogenated (ortho > para > meta). Loss of halogen is favored by higher reaction temperatures and retarded by increasing hydrogen pressure. Acidity in the form of acid addition or an acidic catalyst will tend to inhibit dehalogenation. The use of various modifiers has been reported to increase selectivity. These include sulfur containing compounds, MgO and organic bases. A number of promoters have been used to either increase the rate of halonitroaromatic hydrogenations or to limit the amount of accumulated hydroxylamine intermediate. These include a range of vanadium, iron and ruthenium compounds[1]. Solvents can have a marked influence on both the reaction rate and the selectivity to the haloamine. In general, aprotic solvents inhibit dehalogenation and protic solvents tend to increase reaction rate.

| Reaction | Temperature (°C) | Pressure (bar) | Solvent | Catalyst | Catalyst Recommendation |
|---|---|---|---|---|---|
| Halonitro → haloamine | 5-50 | 1-5 | Alcohols, cyclohexane or ethyl acetate | Pt/C | B101032-3, B103032-3, B102032-1, B101038-1, B105047-1, 1R18MA, 1R117, 1R128M, 3R128M |

[1] Theodoridis, G.; Manfredi, M.C.; Krebs, J.D. *Tetrahedron Lett.* **1990**, *31*, 6141.

## 4.1.6 Reductive Alkylation

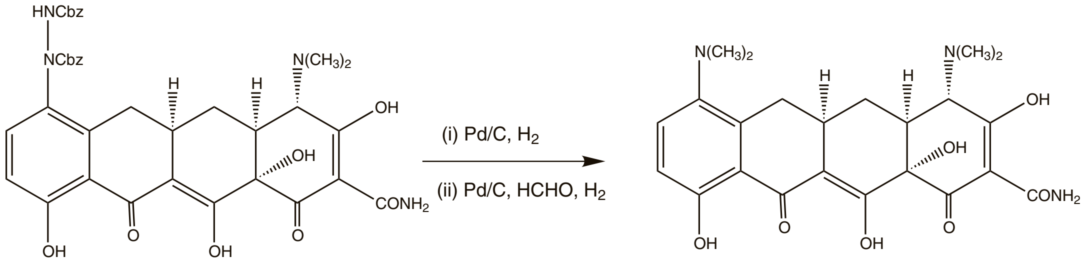
Reductive alkylation involves the reaction of a primary or secondary amine with an aldehyde or ketone to form a secondary or tertiary amine respectively. Formation of the imine intermediate is favored by acidic conditions. The imine intermediate is seldom isolated.

The secondary amine products from this reaction are also suitable substrates for further alkylation. Thus, when wanting to produce a secondary amine (with a minimum of tertiary amine) from a primary amine feedstock, the carbonyl to primary amine molar ratio should not exceed one.

In some cases, the amine may be produced *in-situ* from the corresponding nitro or nitroso compound. Similarly the carbonyl may, in some circumstances, be produced *in-situ* from the appropriate acetal, ketal, phenol or alcohol. Aldehydes are generally more reactive than ketones because they tend to be less sterically hindered. Pt or Pd catalysts are generally preferred for reductive alkylations.

Where possible it is best to pre-form the imine by condensation of the amine and carbonyl compound before hydrogenation commences. This limits the extent of carbonyl hydrogenation that occurs. A catalyst of high selectivity is required to minimize hydrogenation of the carbonyl compound to the alcohol prior to imine formation via condensation. Sulfided platinum catalysts can be used to minimize alcohol formation but generally require more severe operating conditions. Non-sulfided Pt catalysts are effective under mild reaction conditions (10 bar, 100°C).

A reductive alkylation of commercial significance in the pharmaceutical area is the methylation of 8 amino tetracycline to produce Minocycline. This is an example of the 'telescoping' of 2 catalytic stages whereby the amino group in the precursor material is deprotected and then alkylated by addition of formaldehyde using the same Pd/C catalyst:



| Reaction | Temperature (°C) | Pressure (bar) | Solvent | Catalyst | Catalyst Recommendation |
|---|---|---|---|---|---|
| from aldehyde | 20–100 | 1–50 | Alcohol or the aldehyde | Pd/C | A109047-5, A503032-5, A503023-5, A102023-5, 5R338M, 5R58, 5R39 |
| | | | | Ni | A-5000 |
| | | | | Ni/Mo | A-7000 |
| | | | | Pt/C | B102032-3, B104032-3, B105032-3, B106032-3, 5R18MA, 5R117, 5R128M |
| from ketone | 50–150 | 1–50 | Alcohol or the ketone | Pd/C | A109047-5, A503032-5, A503023-5, A102023-5, 5R338M, 5R58, 5R39 |
| | | | | Ni | A-5000 |
| | | | | Ni/Mo | A-7000 |
| | | | | Pt/C | B102032-3, B104032-3, B105032-3, B106032-3, 5R18MA, 5R117, 5R128M |

## 4.1.7 Reductive Aminations

This reaction is essentially the same as a reductive alkylation except that the "amine" feedstock employed is ammonia. The catalyst of choice is similar to that above. Co and Ni are most selective for primary amines with Pd and Pt tending to give a considerable proportion of secondary amine. Excess ammonia is employed to suppress hydrogenation of the carbonyl to the corresponding alcohol.

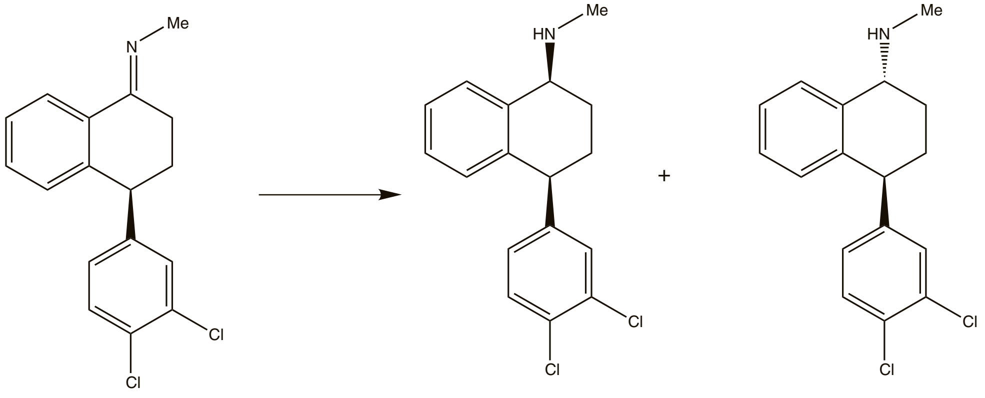
| Reaction | Temperature (°C) | Pressure (bar) | Solvent | Catalyst | Catalyst Recommendation |
|---|---|---|---|---|---|
| from aldehyde | 50–300 | 1–50 | None or alcohol | Pd/C | A109047-5, A503032-5, A503023-5, A102023-5, 5R338M, 5R58, 5R39, 5R434 |
| from ketone | 50–300 | 10–50 | None or alcohol | Pd/C | A109047-5, A503032-5, A503023-5, A102023-5, 5R338M, 5R58, 5R39, 5R434 |

## 4.1.8 Imines

Reductive alkylations/aminations involve the condensation of a carbonyl compound with an amine to form an imine or aminol intermediate, which undergoes hydrogenation to the amine. In some cases, the imine is the feedstock for hydrogenation. Pd and Pt heterogeneous catalysts are typically used although homogeneous Ir catalysts are also effective. Pd and Pt catalysts can be used under relatively mild operating conditions of 20–100°C and 1–10 bar pressure. Alcohols are usually the solvents of choice and acidic conditions often promote the reaction.

This process is operated commercially in the production of the anti-depressant Sertraline and catalyst selection is crucial in maximizing selectivity to the desired cis isomer. The final step in this process is the resolution of the cis enantiomeric pair to give the desired 1S,4S product.

Homogeneous Ir catalysts have also been employed with chiral diphosphine ligands in the asymmetric hydrogenation of imines (See Section 4.9.1).

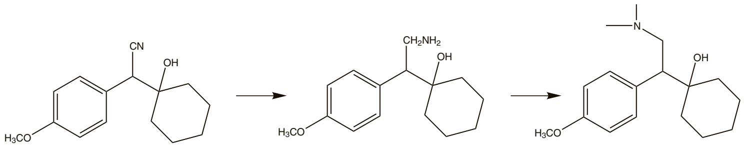


| Reaction | Temperature (°C) | Pressure (bar) | Solvent | Catalyst | Catalyst Recommendation |
|---|---|---|---|---|---|
| Imine → amine | 20–100 | 1–10 | Alcohol or toluene | Pd/C | A109047-5, A503023-5, A503032-5, A102023-5, 5R338M, 5R434, 5R394, 5R39 |
| | | | | Pt/C | B103032-5, B501032-5, 5R128M, 5R103 |

## 4.1.9 Nitriles

The catalytic hydrogenation of nitriles is widely used for the preparation of primary amines. Many different metallic catalysts have been employed for this duty but amongst the most effective are Ni, Co, Pd, Rh and Pt.

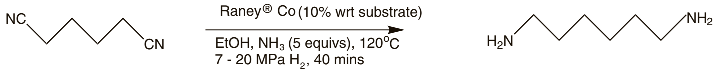
Unwanted secondary or tertiary amines can be formed via the reaction of the desired product with the intermediate imine and control of the reaction conditions is critical to achieve high selectivity.



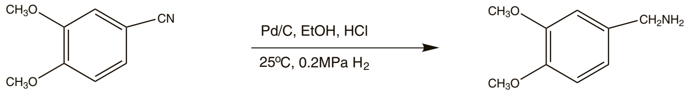
**Venlafaxine**

An example of a commercial application of this chemistry is the hydrogenation and alkylation to produce the anti-depressant Venlafaxine. Both Ni and Pd have been used on large scale for this conversion.

When employing the widely-used base metal catalysts (Ni and Co), alkali or ammoniacal conditions often give the best selectivity for the primary amines. For example, excellent yields of 1,6 hexanediamine were obtained in the hydrogenation of adiponitrile over Raney Co:

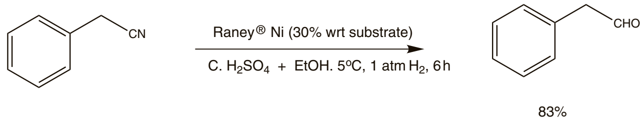


When supported PGM catalysts are used for the formation of the primary amines, either acidic solvent conditions (at least 2–3 moles of acid/mole of nitrile) or excess ammonia (>2 moles/mole nitrile) are employed. Formation of secondary amines is favored by neutral conditions while tertiary amines are usually produced predominantly only in the presence of a low molecular weight secondary amine.



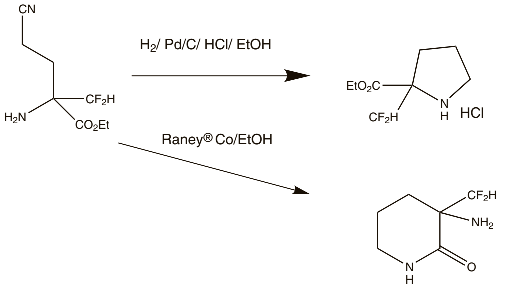
For aromatic nitriles in ammonia or acidic media, Pd and Pt are preferred for the production of primary amines. In neutral solvents, Pt and Rh are preferred for the formation of secondary amines and Pd for the production of tertiary amines.

In acidic, aqueous media, nitriles can undergo reductive hydrolysis of the imine intermediate to yield aldehydes and/or alcohols in average yield. Ni or Pd are the catalysts of choice for this reaction, which can be affected at RT and 1 bar $H_2$ pressure.



The solvent is acidified with sulfuric acid. The acid promotes the hydrolysis of the imine and acts as a scavenger for the ammonia. In order to force the reaction to the desired aldehyde, phenylhydrazine or semicarbazide can be added. The aldehyde forms the respective condensation phenylhydrazone or semicarbazone product. At least 1–2 moles of additive/mole of aldehyde needs to be added.

Reductive cyclization may also be an important reaction pathway when a suitable second reactive functional group is available. For example, it has been reported that under hydrogenation conditions aminonitrile or cyano esters can undergo intramolecular cyclization reaction to give a pyrrolidine (amino group reacts with a cyano group) or a piperidone (amine group reacts with an ester group). Selectivity is highly catalyst dependent.[1]



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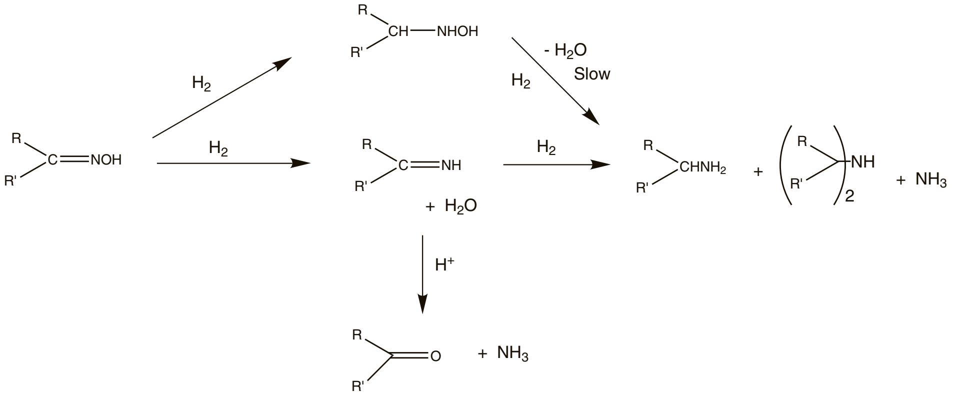
[1] Zhu, J.; Price, B.A.; Walker, J.; Zhao, S.X. *Tetrahedron Lett.* **2005**, *46*, 2795.

| Reaction | Temperature (°C) | Pressure (bar) | Solvent | Catalyst | Catalyst Recommendation |
|---|---|---|---|---|---|
| ***to Aliphatic Amine*** | | | | | |
| 1°–amine $RNH_2$ | 5–100 | 1–10 | Alcohol/ammonia or alcohol/min. acid or acetic anhydride | Pd/C | A503023-5, A503032-5, A102023-5, 5R338M, 5R394, 5R434 |
| | | | | Pt/C | B103032-5, B501032-5, 5R128M, 5R103 |
| | | | | Rh/C | C101023-5, C101038-5, 5R20A, 5R590 |
| | | | | Ni | A4000, A5000, A7000, A7063 |
| | | | | | AMCAT 5<br>AMCAT 7 |
| 2°–amine $R_2NH$ | 50–100 | 2–5 | Alcohols. Neutral conditions. | Rh/C | C101023-5, C101038-5, 5R20A, 5R590 |
| | | | | Pd/C | A503023-5, A503032-5, A102023-5, 5R338M, 5R434, 5R487 |
| 3°–amine $R_3N$ | 50–100 | 2–5 | Alcohols, or DMF with 2°–amine | Pd/C | A503023-5, A503032-5, A102023-5, 5R338M, 5R434, 5R487 |
| | | | | Pt/C | B103032-5, B501032-5, 5R128M,5R103 |
| ***to Aromatic Amine*** | | | | | |
| 1°–amine $ArNH_2$ | 50–100 | 1–10 | Alcohol/ammonia or alcohol/min. acid or acetic anhydride | Pd/C | A503023-5, A503032-5, A102023-5, 5R338M, 5R434, 5R487 |
| | | | | Pt/C | B103032-5, B501032-5, 5R128M, 5R103 |
| 2°–amine $Ar_2NH$ | 5–100 | 2–5 | Alcohol/water | Pt/C | B103032-5, B501032-5, 5R128M, 5R103 |
| 3°–amine $Ar_3N$ | 50-100 | 2–5 | Alcohol or DMF with 2°–amine | Pd/C | A503023-5, A503032-5. A102023-5, 5R338M, 5R434, 5R487 |
| | | | | Pt/C | B103032-5, B501032-5, 5R128M, 5R103 |
| ***to Aldehyde*** | 30–100 | 1–5 | Alcohol/acid or water/acid | Pd/C | A402002-5, A109047-5, A503023-5, 5R39, 5R434, 5R374 |

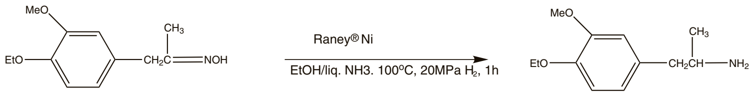
## 4.1.10 Oximes

Hydrogenation of oximes to amines usually proceeds through the corresponding imines as intermediates, which can give rise to secondary amines, or via hydrolysis, to carbonyl compounds or alcohols.



Of the Platinum Group Metals, Rh is the preferred catalytic metal for the formation of primary amines, usually producing less secondary amine product than Pd. Acidic or ammoniacal solvents favor the formation of primary amines by suppressing reductive coupling side reactions. Acidic conditions are recommended to minimize reaction rate inhibition caused by the amine products. When using a Rh catalyst, the amount of acid is not critical, but with a Pd catalyst, there should be at least 2–3 moles of acid per mole of oxime.

The base metals Ni and Co have also been widely used for this chemistry and a comparative study showed Raney Co gave best selectivity to primary amines and could be used without addition of base or ammonia. Raney Ni on the other hand tends to work best when these additives are used.



Pt or Pd catalysts are generally preferred for the partial hydrogenation of ketoximes or their O-alkylated derivatives to the corresponding hydroxylamine.

| **Reaction** | **Temperature (°C)** | **Pressure (bar)** | **Solvent** | **Catalyst** | **Catalyst Recommendation** |
|---|---|---|---|---|---|
| oxime → amine | 30–60 | 1–5 | Alcohol/acid | Pd/C | A109047-5, A503023-5, A503032-5, A102023-5, 5R58, 5R434, 5R338M |
| | | | | Rh/C | C101023-5, C101038-5<br>5R20A |
| | | | | Ni | A-4000, A-5000, A-7000 |

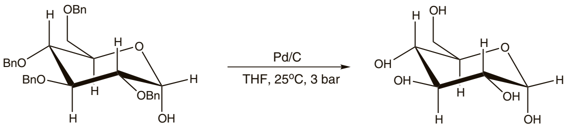
## 4.1.11 Hydrogenolysis

### a. Deprotection Reactions

In the manufacture of pharmaceuticals and fine chemicals there is often a requirement for a protection strategy to minimize possible side reactions during a synthesis. Small, easily removed protection, available for a range of functional groups, is highly desired. One such easily removed protection is derived from the facile catalytic hydrogenolysis of benzylic groups. The classic functional groups requiring protection are alcohols, acids and amines.

Cleavage of the benzyl-oxygen bond of benzyl alcohols, ethers and esters, or the benzyl-nitrogen bond of benzyl amines and amides by catalytic hydrogenation can be performed with good selectivity under mild conditions using a heterogeneous Palladium on Carbon (Pd/C) catalyst in the presence of hydrogen gas or a hydrogen transfer agent, e.g. ammonium formate or isopropanol. Efficient removal depends on selection of the most active and selective catalyst, and an optimized set of reaction conditions[1]. A variety of solvents, temperatures, pressures and catalyst loadings should be evaluated to arrive at an optimized set of reaction conditions. Increased reaction temperature and decreased reaction pressure promote hydrogenolysis. The addition of acid facilitates reaction. Hydrogenolysis of the less bulky benzyl group occurs in most cases. Simple olefins, enol ethers, acetylenes and nitro groups are often hydrogenated in preference to the cleavage of benzyl ethers or benzyl amines.

### O–Debenzylation

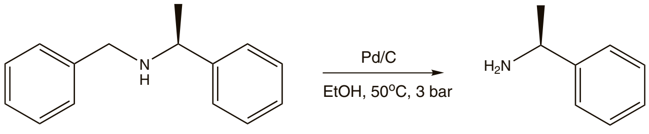


**The debenzylation of 2,3,4,6-tetra-O-benzyl-D-glucopyranose**

Typical reaction conditions for an O-debenzylation are 20 to 30°C and 25 to 50 psi $H_2$ pressure. The classical Pd/C catalyst used for this reaction is Pearlman's catalyst (a 20% palladium hydroxide on carbon catalyst), but in most cases it is possible to use a catalyst with a much lower Pd content as a range of more active and selective catalysts with reduced metal loadings have been developed. Solvent choice is critical. Commonly employed solvents are THF, ethanol, ethyl acetate and acetic acid. Reaction rates are often fastest in THF. Catalyst design effects are important for catalyst performance. Catalysts with eggshell metal distributions which are unreduced typically perform better than uniform metal distribution and/or reduced catalysts.

### N–Debenzylation

N-debenzylations are usually more difficult to perform than O-debenzylations. Typical reaction conditions for a N-debenzylation are 50 to 60°C and 25 to 50 psi $H_2$ pressure.

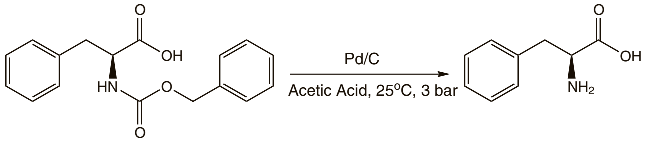


**The debenzylation of N-benzyl N-α-methyl benzylamine**

Solvent choice is critical. For amine deprotection, the free amine products are well known to adsorb at active metal sites, inhibiting or even completely poisoning the catalyst. The presence of acid in the reaction solution helps to prevent catalyst inhibition through the protonation of the amine product. Commonly employed solvents are ethanol, ethyl acetate, acetic acid and alcohol/acid solvent mixtures. Both unreduced and reduced metal, eggshell metal distribution catalysts perform well.

### Removal of Carbobenzyloxy Protecting Groups

Typical reaction conditions for the removal of a carbobenzyloxy (Cbz) protecting group are 25 to 35°C and 25 to 50 psi $H_2$ pressure. It is not possible to accurately follow the course of reaction by hydrogen uptake as for the removal of a Cbz protecting group 1 mole of carbon dioxide is generated for each mole of hydrogen consumed. Solvent choice is again critical with considerations similar to that for a N-debenzylation. The presence of acid in the reaction solution helps to prevent catalyst inhibition through the protonation of the amine product. Commonly employed solvents are methanol, ethanol, ethyl acetate, acetic acid and alcohol/acid solvent mixtures. Both unreduced and reduced metal, eggshell metal distribution catalysts perform well.



**The deprotection of N-benzyloxycarbonyl-L-phenylalanine**

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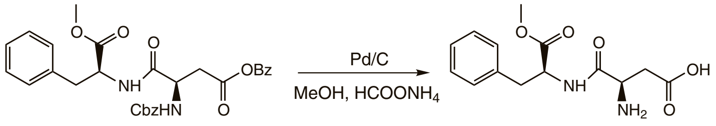
[1] McNair, R. J. *Specialty Chemicals Magazine*, December 2006, 30.

## Deprotection Reactions via Transfer Hydrogenation

The use of a hydrogen donor rather than gas phase hydrogen has many processing advantages including: no pressure equipment requirement; no need for $H_2$ storage, delivery systems or gas measurement; the use of standard vessels and equipment; and potential chemoselectivity advantages (e.g. deprotection in the presence of an aryl chloride). Different and often beneficial reaction selectivity can be observed during catalytic hydrogenation using a hydrogen transfer agent instead of hydrogen gas.

Typical reaction conditions for a deprotection reaction via transfer hydrogenation are solvent reflux or 50°C under atmospheric nitrogen. Both solvent and hydrogen transfer agent choice are critical. Commonly employed solvents are methanol, ethanol, ethyl acetate, THF and/or water. Commonly employed hydrogen transfer agents are ammonium formate, sodium hypophosphite hydrate and hydrazine hydrate. Typically more than 1 equivalent of a hydrogen donor is required as some decomposition of the transfer agent over the catalyst occurs.



**The deprotection of O-benzyl-N-benzyloxycarbonyl-L-aspartame**

| Reaction | Temperature (°C) | Pressure (bar) | Solvent | Catalyst | Catalyst Recommendation |
|---|---|---|---|---|---|
| O-Debenzylation | 5–50 | 1–10 | THF, ethyl acetate, alcohols | Pd/C | A405028-5, A405032-5, A503023-5, A503032-5, 5R39, 5R393, 5R440 |
| N-Debenzylation | 30-100 | 1–10 | Alcohol/mineral acid, acetic acid, ethyl acetate | Pd/C | A405028-5, A405032-5, A503032-5, A503023-5, 5R39, 5R434, 5R487 |
| Removal of Carbobenzyloxy Protecting Groups | 5–50 | 1–10 | Alcohol/mineral acid, acetic acid, ethyl acetate | Pd/C | A405028-5, A405032-5, A503023-5, A503032-5, 5R39, 5R39, 5R434, 5R487 |
| Deprotection Reactions via Hydrogen Transfer | 30-100 | Ammonium formate, formic acid | Alcohols, THF | Pd/C | A503023-5, A503032-5, A402028-10, A501023-10, A501032-10, 5R338M, 5R434, 10R39, 10R487, 5T401 |

## b. Hydrodehalogenations

Hydrogenolytic cleavage of carbon-halogen bonds is normally carried out with either Pd or Ni catalysts under relatively mild reaction conditions (5 – 100ºC, 1 – 10 bar $H_2$ pressure).

$RX + H_2 \rightarrow RH + HX$
X = F, Cl, Br, I

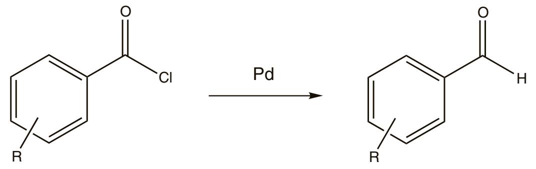
Pd is the most active and preferred catalytic metal. With Ni catalysts, because of the poisoning properties of the released halide ion, large catalyst loadings are required. The ease of dehalogenation depends on the halogen (I > Br > Cl > F) and on other functional groups in the molecule. Selective hydrodehalogenation is possible in some cases, e.g. removal of chlorine with fluorine retention. Dehalogenation is accelerated by the presence of neighboring electron-withdrawing groups. Alkyl halides are removed less readily than are benzyl or aryl halides.

Solvents can have a marked influence on the reaction rate. The use of polar, hydrolytic solvents, and the addition and presence of base increase reaction rate. The reaction rate is often adversely affected by the release of halide ion. A basic halide acceptor is usually added to the reaction for this reason. Bases typically used to promote the reaction are KOH, $Na_2CO_3$, MgO and triethylamine. At least 2 equivalents of base per equivalent of halide should be added. Acidity in the form of acid addition or an acidic catalyst will tend to inhibit dehalogenation. Loss of halogen is favored by higher reaction temperatures and retarded by increasing hydrogen pressure.

## c. Rosenmund Reduction

The Pd catalyzed hydrogenolysis of acyl chlorides to the corresponding aldehyde is referred to as the Rosenmund reduction. It is a standard method for the conversion of carboxylic acids to aldehydes.

The transformation is typically carried out using either a $Pd/BaSO_4$ or Pd/Carbon catalyst under mild reaction conditions (temperatures of 5–50°C and pressures of 1–3 bar hydrogen). The reaction temperature should be kept at the minimum level required for the dehalogenation in order to prevent over hydrogenation of the carbonyl group to the primary alcohol. Aryl aldehyde products are easier to over reduce than are aliphatic aldehydes. The reaction must be carried out in the absence of water otherwise unwanted hydrolysis of the acyl chloride starting material to the corresponding carboxylic acid will occur. Dry catalysts must therefore be used to maintain the anhydrous conditions. Nitrogen or sulfur-containing compounds are often added to the reaction mixture to modify the catalyst to increase selectivity to the aldehyde and to prevent over reduction. Typical additives include thiourea, thioquinanthrene, tetramethylthiourea and quinoline-sulfur. These added inhibitors can also prevent unwanted reduction or hydrogenolysis of other functional groups in the molecule (for example olefins or aryl halogens). As with other hydrodechlorinations, a basic chloride acceptor is often utilized. Typical chloride acceptors include 1,2-butylene oxide, aliphatic amines, sodium carbonate, magnesium oxide and 2,6–dimethylpyridine (at least 2 equivalents per equivalent of halide). Sometimes, due to the ease of acid chloride hydrodechlorinations, it is possible to remove the liberated HCl with a nitrogen sparge or by operating at subatmospheric pressures so that the addition of a specific chloride acceptor is not necessary.



| Reaction | Temperature (°C) | Pressure (bar) | Solvent | Catalyst | Catalyst Recommendation |
|---|---|---|---|---|---|
| Hydrodehalogenation | 5-100 | 1–10 | Alcohols, ethyl acetate or vapor phase | Pd/C | A405028-5, A503023-5, A503038-5, A503129-5, 5R39, 5R435, 5R487 |
| Rosenmund Reduction | 5–50 | 1–3 | Toluene, xylene, acetone or THF | Pd/C | A302023-5, A302038-5, A302085-5, 5R435, 5R487 |
| | | | | $Pd/BaSO_4$ | A308053-5, A201053-5, 5R29A |

## 4.1.12 Transfer Hydrogenations[1]

When hydrogen gas and/or hydrogenation plant is not readily available, then a hydrogenation may be achieved using a chemical hydrogen donor. In effect the catalyst dehydrogenates the donor molecule to generate hydrogen to carry out the hydrogenation. The donor molecule and catalyst should be selected with care so that the rate of hydrogen release is comparable to the rate of hydrogenation of the feedstock. Typical donor molecules include cyclohexene, formates, phosphinates, propan–2–ol and indolene.

The use of a hydrogen donor rather than gas phase hydrogen can have processing advantages including: no pressure equipment requirement; no need for $H_2$ storage, delivery systems or gas measurement; the use of standard vessels and equipment; and potential chemoselectivity advantages (e.g. deprotection in the presence of an aryl chloride). Different and often beneficial reaction selectivity can be observed during catalytic hydrogenation using a hydrogen transfer agent instead of hydrogen gas.

Heterogeneous Pd and Pt catalysts are usually the catalysts of choice for transfer hydrogenations. Reactions are typically performed at solvent reflux under atmospheric nitrogen but it is possible to operate at lower temperatures when required. Both solvent and hydrogen transfer agent choice are critical. Commonly employed solvents are methanol, ethanol, ethyl acetate, THF and/or water. Commonly employed hydrogen transfer agents are ammonium formate, sodium hypophosphite hydrate and hydrazine hydrate. Typically more than 1 equivalent of a hydrogen donor is required as some decomposition of the transfer agent over the catalyst occurs.

Transfer hydrogenation can be accomplished using homogeneous catalysts. For example, tetralone has been hydrogenated with Rh-120 with an amine ligand in the presence of a hydrogen donor, propan-2-ol. Examples of PGM precursors of homogeneous catalysts used for transfer hydrogenations in the literature are Iridium (Ir-93 $[IrCl(COD)]_2$), Rhodium (Rh-93 $[RhCl(COD)]_2$), (Rh-120 $[RhCl_2(CP^*)]_2$) and Ruthenium (Ru-120 $[RuCl_2(pcymene)]_2$). Please refer to section 4.9.1 for information on asymmetric hydrogenation.

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[1] R.A.W. Johnstone et al. Chem. Rev. (1985) 85 129–170.

| Reactant | Product | Donor | Solvent | Temperature (˚C) | Catalyst | Catalyst Reaction |
|---|---|---|---|---|---|---|
| Nitro | Amine | Formic acid, phosphinic acid, sodium formate, sodium phosphinate, tetraethyl ammonium formate | Methanol, ethanol or THF | 50–80 | Pd/C | A503023-5, A503038-5, A102023-5, A102038-5, 5R487, 5R338M, 5R434 |
| Halonitro | Haloamine | Formic acid, phosphinic acid, sodium phosphite | Methanol, ethanol or water | 60–80 | Pt/C | B101032-3, B103032-3, B102032-1, B101038-1, B105047-1, 3R128M, 3R18MA,1R117, 1R128M |
| Imine | Amine | Formic acid & Et$_3$N, propan–2–ol | None or acetonitrile | 0–60 | Ir | 93 |
| | | | | | Rh | 93, 120 |
| Alkene | Alkane | Cyclohexene, indolene, triethyl ammonium formate | None | Reflux | Pd/C | A503023-5, A503038-5, A102023-5, A102038-5, 5R87L, 5R434, 5R338M |
| Carbonyl | Alcohol | Cyclohexene, phosphinic acid, sodium phosphinate | Ethanol or THF | Reflux | Pd/C | A503023-5, A503038-5, A102023-5, A102038-5, 5R487, 5R434, 5R338M |
| Ketone | Alcohol | Formic acid & Et$_3$N, propan–2–ol | None or acetonitrile | 0–60 | Ir | 93 |
| | | | | | Rh | 93, 120 |
| Deprotection Reactions via Hydrogen Transfer | | Ammonium formate, formic acid | Alcohols or THF | 30-100 | Pd/C | A503023-5, A503032-5, A402028-10, A501023-10 A501032-10, A501032-10, 5R338M, 5R434 10R39, 10R487, 5T401 |

## 4.2 DEHYDROGENATION

Catalytic thermal dehydrogenation is an endothermic process, and hence high operating temperatures (up to 350°C) and high catalyst loadings (3–10% with respect to feedstock) are often necessary. At such high temperatures, most PGM complexes decompose, so homogeneously-catalyzed dehydrogenations in the liquid phase are usually not feasible.

The reaction is often an equilibrium limited process and so in order to drive the process to the desired products the hydrogen must be removed from the process. Traditionally, nitrogen has been used to purge the liberated hydrogen from the reaction, but increasingly the use of hydrogen acceptors is finding favor. Hydrogen acceptors should be used in 0.5–2.0 molar quantities with respect to the liberated hydrogen. Where the products include water, e.g. when using nitrobenzene as acceptor, care should be taken, because the steam that is liberated can cause bumping of the reactor contents in liquid phase reactions. For this reason, it is desirable to use dry powder catalysts for liquid phase reactions and dry pelleted catalysts for gas phase

| Hydrogen Acceptor | Product |
|---|---|
| Nitrotoluene | Toluidine (+ water) |
| Nitrobenzene | Aniline (+ water) |
| Maleic acid | Succinic acid |
| Dimethylmaleate | Dimethylsuccinate |
| α–methylstyrene | Cumene |
| trans–stilbene | Dibenzyl |
| Tetralin | Decalin |
| Indene | Indane |

reactions. The use of a hydrogen acceptor will often lead to improved thermodynamics for the whole system which should allow the use of lower operating temperatures and lower by-product formation. Typical high boiling point solvents used include biphenyl and polyglycol ethers. It is possible sometimes to use the hydrogen acceptor as the solvent.

The ease of dehydrogenation is dependent on the substrate and operating conditions. However, the following general comments can be made:

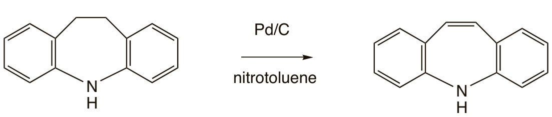
- the reaction is easier if at least one double bond is close to the dehydrogenation site
- the reaction is easier if the end product is a fully aromatic compound
- 6 and 7-membered or larger ring systems are easier to dehydrogenate than 5-membered rings

The catalysts of choice for liquid phase dehydrogenations are Pd > Pt > Rh.

Catalyst performance can be enhanced by the addition of inorganic bases such as $Na_2CO_3$, MgO (up to about 5% by weight with respect to the catalyst). Addition of base neutralizes any acidic sites on the catalyst, which if left untreated, could cause by–product formation.

Very small additions (2–10 ppm with respect to the feedstock) of organic sulfur compounds such as diphenyl sulfide can promote some dehydrogenation reactions. Such additions have to be very carefully optimized.

A particular dehydrogenation of industrial importance is the formation of iminostilbene from iminodibenzyl :



The product is an intermediate in the preparation of Carbamazepine – a treatment for epilepsy.

For the dehydrogenation of cyclohexanols and cyclohexanones, the favored hydrogen acceptors are olefins e.g. alpha–methylstyrene.

A common problem with operating catalysts at high temperatures in the vapor phase for extended periods is that coking may occur. This has the effect of partially masking the metal surface and so reducing activity but may be beneficial in terms of selectivity. One way of reducing this effect on the Pd or Pt pelleted catalysts is to introduce a small quantity of hydrogen into the feedstock.

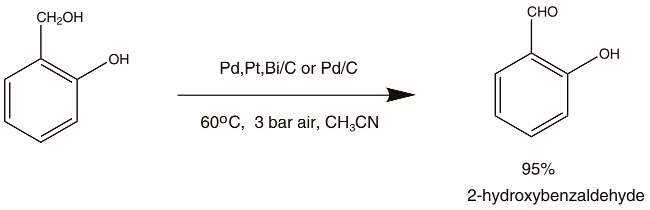
| **Reaction** | **Temperature (°C)** | **Solvent** | **$H_2$ Acceptor** | **Catalyst** | **Catalyst Recommendation** |
|---|---|---|---|---|---|
| Cyclohexanones or Cyclohexanols to Phenols | 180–275 | biphenyl | Olefinic (e.g. α-methylstyrene or tetralin) | Pd/C | A503023-5, A503038-5, A102023-5, A102038-5, A501023-10, A501038-10, A101023-10, A101038-10, 5R87L, 5R487, 5R434, 10R87L, 10R487 |
| Alkane to Alkene | 180–250 | Glycol, PEG | Nitrotoluene or nitrobenzene | Pd/C | A503023-5, A503038-5, A102023-5, A102038-5, A501023-10, A501038-10, A101023-10, A101038-10, 5R87L, 5R487, 5R434, 10R87L, 10R487 |
| Alcohol to Carbonyl | >200 | None (vapor phase) | None | Pt/C | B103032-5, B103018-5, B501032-5, 5R128M, 5R18 |
| | | | | Ni/Mo | A-7000<br>A-7200 |

## 4.3 OXIDATIVE DEHYDROGENATION

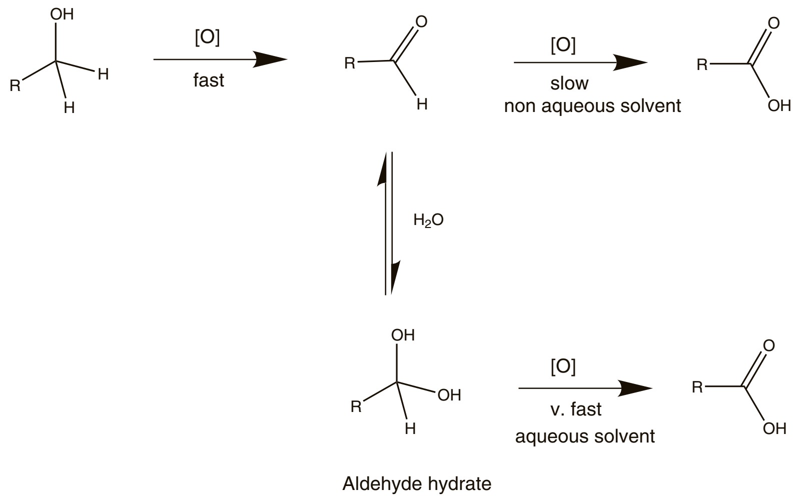
An alternative way of improving the thermodynamics of dehydrogenation processes is to use oxygen as the hydrogen acceptor, so yielding water as a by-product. This technique has been successfully employed in the oxidation (or oxidative dehydrogenation) of alcohols to yield carbonyl compounds and/or carboxylic acids.

Ru, Pt and Pd catalysts have all been used for these oxidations. Aliphatic alcohols often work best with Pt or Ru catalysts. Ru tends to give better selectivity to the carbonyl compound whereas Pt can give further reaction to the carboxylic acid. The activity of Pt catalysts can often be enhanced by the addition of a promoter such as Bismuth (e.g. 5% Pt, 1.5% Bi/C Type 160).

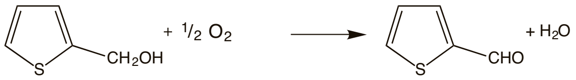
If the substrate is an aromatic alcohol then the most active catalyst is often Pd or Pt or a combination of these metals (e.g. 4%Pd, 1%Pt, 3%Bi/C Type 430).



Selectivity to the carbonyl compound is often enhanced by the use of organic solvents that are immiscible with water eg. toluene, xylene, DCE etc.. Aqueous solvents tend to enhance the further reaction of the carbonyl to the carboxylic acid via the formation of the hydrate.



In contrast to hydrogenation systems, sulfur-containing moieties do not appear to poison PGM catalysts under oxidation conditions. For example, 2-thienylmethanol can be readily oxidized to the corresponding aldehyde in > 90% yield with a Pt/C catalyst in toluene. Furthermore, the catalyst can be re-used several times.



Supported Pd, Pt or mixed-metal catalysts incorporating Bi have been used in aqueous solution at 40 – 60°C for the air oxidation of sugars to the corresponding mono-acid. e.g. glucose to gluconic acid . This reaction is favored by the use of alkaline conditions, typically pH 8-10.

Poisoning of the Pt catalyst can occur by over-oxidation of the metal surface to form a Pt oxide species. This effect can be minimized by:

- Control of oxygen availability (often by operating at low partial pressures of oxygen)
- pH optimization by continuous addition of base as the reaction proceeds
- periodic regeneration of the catalyst with a washing/ reduction treatment

**Note: When operating any metal catalyzed process a full hazard and operability study is recommended. With catalytic oxidation processes the study needs to consider the hazards arising from both complete combustion and explosion.**

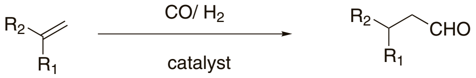
| Reaction | Temperature | Solvent (°C) | $H_2$ Acceptor | Catalyst | Catalyst Recommendation |
|---|---|---|---|---|---|
| Alcohol to carbonyl | 50-80 | 2-5 | Toluene or acetonitrile | Ru/C | D101023-5, D101002-5, 5R97 |
|  |  |  |  | Pt/C | B103032-5, B501032-5, 5R128M |
|  |  |  |  | Pt(Bi)/C | B503032-5, B111022-5, 5R160 |
|  |  |  |  | Pd,Pt(Bi)/C | 5R430 |
| Primary alcohol or aldehyde to acid | 50-80 | 2-5 | water + base | Pt(Bi)/C | B503032-5, B111022-5, 5R160 |
|  |  |  |  | Pd/C | 5R487 |

## 4.4 CARBONYLATION

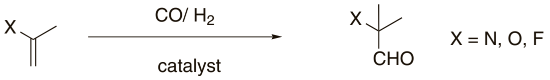
The general descriptor "Carbonylation" covers a wide variety of reactions in which carbon monoxide adds a carbonyl-based functional group to organic molecules. The reaction, at one level, represents one of the largest scale precious metal catalyzed homogeneous processes (Hydroformylation). At a much smaller scale it provides researchers with a very adaptable route into products such as carboxylic acids, and esters, aryl aldehydes and aryl amides.

### Hydroformylation

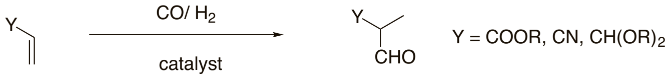
Rhodium-catalyzed hydroformylation is an industrial process of fundamental importance.[1] Based on purely steric factors, *gem*-substituted olefins with both aryl and alkyl groups usually have a tendency to give the linear hydroformylation product. They also display lower reaction rates than monosubstituted olefins. The use of bidentate diphosphite or diphosphine ligands in combination with simple rhodium precursors such as [Rh(acac)$(CO)_2$] can give very high linear selectivity.



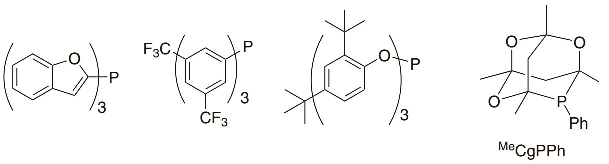
In the case of heteroatom-functionalized alkenes the formyl group is generally introduced next to the heteroatom, although *gem*-disubstituted substrates may also produce some linear products.



Electron poor alkenes give generally the branched product, reflecting the higher stability of the branched alkyl-metal intermediate.



The hydroformylation of acrylate esters has been described in the presence of rhodium catalysts with a variety of phosphorus ligands. Rhodium-catalyzed hydroformylation of ethyl acrylate gives complete branched selectivity in the presence of $(PhO)_3P$ at 30 bar and 40ºC. With the same catalyst, the selectivity can be switched to the opposite complete linear selectivity at 1 bar and 80ºC. To underline the complexity of the reaction, it has also been reported[1] that even at low temperature and high pressure the use of hindered and electron withdrawing phosphate ligands in high ligand to rhodium ratio can reverse the selectivity of the reaction in favor of the linear product. An optimized laboratory procedure for the hydroformylation of neat methyl methacrylate has been recently described by Clarke *et al.*[2] Many ligands (such as triphenylphosphine) were found to give high branched selectivity but often with insufficient reactivity. Some of the most effectives ligands (>99/1 ratio) are depicted below.



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[1] '*Rhodium catalysed hydroformylation*', edited by P.W.N.M. Van Leeuwen and C. Claver, Kluwer Academic Publisahers, 2000.
[2] Clarke, M.L.; Roff, G.J. *Green Chem.* **2007**, *9*, 792.

The hydroformylation of methacrylate has been reported less frequently. The steric bulk of the ester residue, as in the case of t-Butyl methacrylate also favors the linear adduct.[3] The use of rhodium catalysts modified with the ligand $^{Me}$CgPPh has led to the highly branched selective hydroformylation of unsaturated esters.[4] Reetz *et al.* reported the hydroformylation of *t*-butyl methacrylate in the presence of rhodium monodentate phosphorus ligands with maximum branched/linear ratio of around 3/1.[5] Reinius *et al.* reported a branched/linear ratio of 27/1 in the hydroformylation of methyl methacrylate in the presence of [(o-methylthio)phenyl}diphenylphosphine.[6]

$[Rh(acac)(CO)_2]$, **Rh-50**, is the rhodium precursor most used in the recent literature but also other complexes such as $[Rh\,Cl\,(CO)_2]_2$, $[Rh(PPh_3)_3(CO)H]$,[7] or the zwitterionic $[BPh_4]^-$ $[Rh(COD)]^+$ [8] have been employed in the hydroformylation of methylmethacrylate. Non-homogeneous rhodium precursors such as $Rh_2O_3$ in the presence of an electron-rich phosphine ($Bu_3P$) have also been reported for the hydroformylation of unsaturated esters.[9]

## Pd-Catalyzed (Heck) Carbonylation

Since the initial publications on this series of reactions by Richard Heck in 1974[10], many other researchers have contributed to improving the scope of the reaction through extending the range of suitable substrates and moderating the conditions required. Reactions are now effective for conversion of many aryl, heteroaryl, benzylic and vinyl halides and sulfonates.[11]

## Alkoxycarbonylation

Alkoxycarbonylation uses water or alcohols as nucleophiles to form carboxylic acids or esters. The limited interaction of alcohol/alkoxide with the palladium catalyst makes this the most robust of this group of reactions and this is reflected in a significant number of industrial applications[12]. Catalysts with aryl-substituted phosphine ligands (both monodentate, e.g. $PPh_3$, and bidentate, e.g. dppp, dppf) are effective for reacting a wide variety of aryl and heteroaryl iodide, bromide and triflate derivatives. However, alkyl-substituted bisphosphines such as bis(dicyclohexylphosphino)propane are necessary as ligands for the activation of aryl and heteroaryl chlorides and less reactive sulfonates such as tosylate. This is related to the need for oxidative addition of the different substrates to initiate the reaction, a mechanistic step that has been intensively studied in Pd-catalyzed cross coupling. Similar rates for oxidative addition, insertion of CO and the reaction with the nucleophile result in different steps being rate determining for different substrate-catalyst combinations leading to relatively slow reactions in comparison with cross coupling. However, given a suitable choice of catalyst, these reactions can generally be carried out under mild conditions (80-150°C and 0-5 bar CO gas) well suited to industrial application.

## Aminocarbonylation

Aminocarbonylation uses ammonia or amines to form amides and can be carried out using similar conditions to the alkoxycarbonylation, although excess amine acts as an inhibitor of the reaction. One means to overcome this limitation is to use trans-amination of the phenyl ester formed by alkoxycarbonylation with phenoxide[13]. This two-step process provides access to a wide range of derivatives that cannot be obtained directly, e.g. t-butyl, thio- and allyl esters, in addition to amides.

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3 Clarke, M.L. *Tetr.Lett.* **2004**, *45*, 4043.
4 Clarke, M.L.; Roff , G.J. *Chemisty: Eur. J.* **2006**, *12*, 7978.
5 Reetz, M.; Li, X. *Angew.Chem.Int.Ed.* **2005**, *44*, 2962.
6 Reinius, H.K.; Laitinen, R.H.; Krause, A.; Pursianen, J.T. *Catalysis Letters,* **1999**, *60*, 65; Reinius, H.K.; Krause, A. *J.Mol.Catal.* **2000**, *158*, 499.
7 Pittman, C.U.; Honnick, W.D.; Yang, J.J. *J.Org.Chem.* **1980**, 45, 684.
8 Alper, H.; Lee, C.W. *J.Org.Chem.* **1995**, 499, *JACS* **1990**, 3674.
9 Falbe, J.; Huppes, N. *Brennstoff-Chemie* **1967**, *48*, 46; Shell patent, NL 6613226 (1967).
10. (a) Schoenberg, A.; Bartoletti I.; Heck, R.F. *J. Org. Chem.* **1974**, *39*, 3318.
 (b) Schoenberg, A.; Heck, R.F. *J. Org. Chem.* **1974**, *39*, 3327.
 (c) Schoenberg, A.; Heck, R.F. *J. Amer. Chem. Soc.* **1974**, *96*, 7761.
11. Barnard, C.F.J. *Organometallics* **2008**, *27*, 5402.
12. Kollár, L. Ed. Modern Carbonylation Methods: Wiley:Weinheim, 2008.
13. Watson, D.A.; Fan, X.; Buchwald, S.L. *J. Org. Chem.* **2008**, *73*, 7096.

## Reductive Carbonylation

Conditions for the reductive carbonylation forming aldehydes initially described by Heck involved the use of syngas (1:1 $H_2$/CO) at high pressure, *ca.* 100 atmospheres. The reaction proceeds best with monodentate phosphine ligands and recently much lower pressure reactions (ca. 5 bar) for aryl iodides, bromides and triflates were shown to be possible using the bulky alkyl-substituted ligand diadamantyl-n-butylphosphine[14]. Alternative conditions, operating at still lower pressure due to the use of hydride donor reagents such as silanes, are also highly effective for aryl iodides, bromides and triflates. In the latter case, bidentate phosphine ligands such as dppp are more effective than monodentate phosphines, this difference between the processes relating to the different mechanisms of hydride transfer in the formation of the product.

The many variables requiring optimization for these reactions, including the choice of catalyst, solvent and base combination, CO pressure, and temperature, make it appropriate to use modern techniques of parallel testing to achieve this in an efficient manner.

## Pd-Catalyzed Carbonylation of Alkenes and Alkynes

### Alkenes

The reaction of carbon monoxide with alkenes shows remarkable changes in selectivity based on the properties of the ligands bound to Pd, and in particular the bite angle for bisphosphines. With 1,2-bis(di-*t*-butylphosphinomethyl)-benzene alkoxycarbonylation of ethene using methanol yields methyl propanoate, a useful precursor in the preparation of methyl methacrylate[15]. This process has been developed to commercial scale by Lucite International with a 120,000 m.t./year plant operating in Singapore in 2009.

$$CH_2{=}CH_2 + CO + CH_3OH \longrightarrow CH_3CH_2CO_2CH_3$$

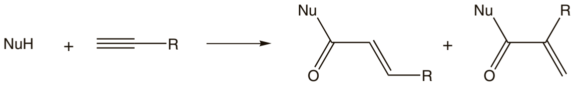
With cationic palladium catalysts having more flexible ligands such as dppp, giving natural bite angles close to 90º, multiple insertions of ethene and carbon monoxide result in chain growth, yielding polyketones with potential application as thermoplastics[16].

$$n\,CH_2{=}CH_2 + n\,CO + CH_3OH \longrightarrow H(CH_2CH_2CO)_nOCH_3$$

For higher alkenes, as for hydroformylation, the formation of linear or branched products is possible, and the branched isomers can be formed enantioselectively. However, in contrast to hydroformylation, this combination of high regio- and enantioselectivity has not yet been achieved using Pd-catalyzed alkoxycarbonylation.

### Alkynes

Carbonylation of alkynes provides a versatile route to a variety of α-β-unsaturated carbonyl derivatives depending on the nucleophilic reagent. For example, reaction with amines yield acrylamides and with thiols yields unsaturated thioesters, and, as for alkenes, high regioselectivity can be obtained for terminal alkynes.



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[14] Klaus, S.; Neumann, H.; Zapf, A.; Strübing, D.; Hübner, S.; Almena, J.; Riermeier, T.; Gross, P.; Sarich, M.; Krahnert, W.-R.; Rossen, K.; Beller, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 154.

[15] Clegg, W.; Eastham, G.R.; Elsegood, M.R.J.; Tooze, R.P; Wang, X.L.; Whiston, K. *Chem. Commun.* **1999**, 1877.

[16] Drent, E.; Budzelaar, P.H.M. *Chem. Rev,* **1996**, 663.

## 4.5 DECARBONYLATION

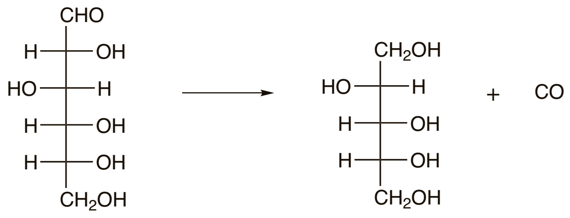
Both Pd and Rh catalysts have been used to decarbonylate aldehydes (to produce alkanes) and acyl chlorides (to produce chloroalkanes or chloroarenes).

$$\mathrm{RCOX} \longrightarrow \mathrm{RX} + \mathrm{CO} \quad (\mathrm{X} = \mathrm{H, Cl})$$

There are also reports of the effective decarbonylation of carboxylic anhydrides, ketones and ketenes.

Dihydrocinnamaldehyde can be decarbonylated with Rh (Rh–40 [$RhCl(CO)(PPh_3)_2$] or Rh–100 [$RhCl(PPh_3)_3$]) to form ethylbenzene[1] in 96% yield.

The decarbonylation reaction can be used to advantage in classical carbohydrate chemistry, exemplified by the one–step synthesis of arabinitol from glucose.



Glucose

Arabinitol

Yields of 90% can be achieved with Rh-100 in N–methylpyrrolidone at 130°C in 30 minutes.[2]

| Reaction | Temperature (°C) | Pressure (bar) | Solvent | Catalyst |
|---|---|---|---|---|
| Decarbonylation of aldehydes,<br>acyl chlorides,<br>carboxylic acid anhydrides,<br>ketones and ketenes | 110–145 | 1 | N–methylpyrrolidone,<br>toluene,<br>benzonitrile or<br>xylene | Rh–100, Rh–40,<br>Rh–93 + chelating diphosphine |

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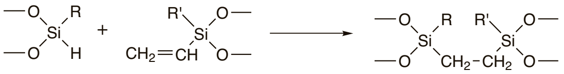
[1] J.M. O'Connor and J. Ma *J. Org. Chem.* **1992**, *57*, 5075.
[2] M.A. Andrews and S.A. Klaeren *Chem. Comm.* **1988**, 1266.

## 4.6 HYDROSILYLATION

Hydrosilylation (often referred to as hydrosilation) is the addition of an H–Si bond across a carbon-carbon double bond.

$$CH_2{=}CHR' \quad + \quad R_3SiH \longrightarrow R_3Si{-}CH_2CH_2R'$$

The reaction finds practical application in the "curing" or hardening of silicone polymers effected by the cross coupling of different silicone fragments.



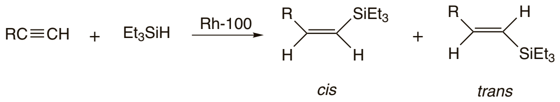
Platinum compounds are extremely active catalysts for this reaction.[1] The catalyst can be used at such low levels that it is not necessary to separate it from the silicone product. Originally, chloroplatinic acid (Speier's catalyst) was used as the most readily available and cheapest hydrosilylation catalyst. However there are two problems:

- chloroplatinic acid is a potent sensitizer and hazardous to health, so great care must be taken during its handling
- chloroplatinic acid contains platinum in oxidation state IV which must be reduced to Pt(0) before it becomes catalytically active. This results in a variable induction period.

A more reliable/reproducible catalyst is Karstedt's catalyst which is made from chloroplatinic acid by the addition of an appropriate siloxane and reducing agent. The Pt is in the Pt(0) oxidation state when used. Johnson Matthey supplies a variety of custom Karstedt's catalysts.

In some cases, specific Pt(II) precursors are used rather than Karstedt's catalyst. Compounds which have been used in this way include Pt-92 $[PtCl_2(cyclohexene)]_2$, Pt-96 $[PtCl_2(COD)]$ and Pt-112 $[PtCl_2(SEt_2)_2]$. Although homogeneous catalysts are commonly used, heterogeneous Pt/C catalysts are effective in some cases.

Rh catalysts can selectively hydrosilylate alkynes to the alkene, but the regiochemistry is very dependent on the solvent used.[2]



| Solvent | % *cis* | % *trans* | others |
|---|---|---|---|
| **Benzene** | 86 | 12 | 2 |
| **Acetonitrile** | 3 | 95 | 2 |

Rh catalysts can also catalyze some hydrosilylation reactions that cannot be catalyzed by Pt complexes[3]. Rh catalysts have also been used to prepare chiral silanes.[4]

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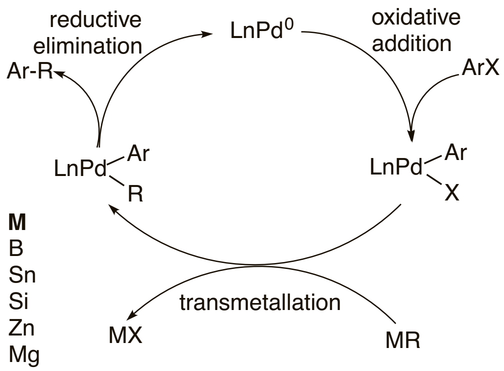
[1] L.N. Lewis *et al.* *Platinum Metals Rev.* **1997**, *41*, 6.
[2] R. Takenchi and N. Tanonchi *J. Chem. Soc. Perkin Trans.* **1994**, 2909.
[3] A.G. Bessmertnykh et al. *J. Org. Chem.* (1997) 62 6069.
[4] K. Tamao *et al.* *J. Am. Chem. Soc.* **1996**, *118*, 12469.

| Reaction | Temperature (°C) | Pressure (bar) | Solvent | Catalyst |
|---|---|---|---|---|
| Hydrosilylation of alkenes | 25–75 | 1 | None or hydrocarbons | Chloroplatinic acid,<br>Pt–92, Pt–96,<br>Pt–112, Pt–114,<br>Pt/Al$_2$O$_3$ B301013-5,<br>B301084-5 |
| Hydrosilylation of alkyne to cis-alkene | 25 | 1 | Ethanol or propan-2-ol | Rh–93, Rh–100 |
| Hydrosilylation of alkyne to trans-alkene | 25 | 1 | Acetonitrile | Rh–93 + PPh$_3$ or<br>Rh–100 |

## 4.7 CROSS-COUPLING REACTIONS

A transition-metal complex, typically a Pd complex, mediated substitution of an aryl, vinyl, or alkyl halide or pseudohalide by a nucleophile is generally referred to as a cross-coupling reaction and typically it follows the oxidative addition, transmetalation, and reductive elimination steps. Although C-C bond forming reactions have been known since the development of Grignard reagents, recent advances by Negishi, Suzuki, Kumada/Tameo have greatly increased the scope and industrial applicability of cross-coupling reations.



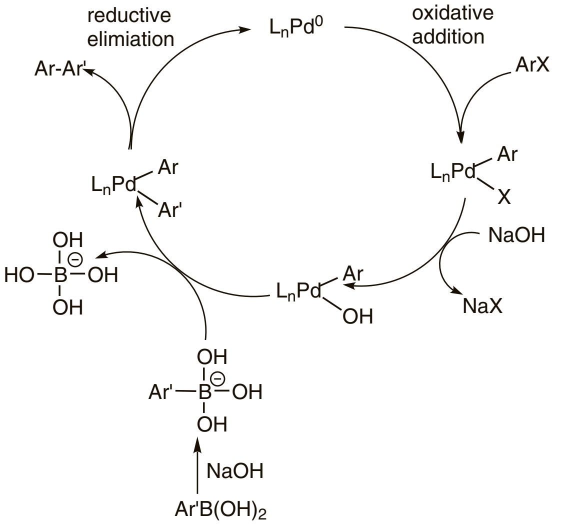
**General Mechanism of Coupling**

This progress in cross-coupling significantly impacted not only academic research, but is widely employed in a variety of synthetic applications, such as the synthesis of natural products, light emitting diodes, liquid crystals, etc. This progress has been greatly facilitated by an increased understanding of the mechanism of these reactions and the development of new ligands. For example Greg Fu's and Koei's independant work on the use of tri *t*-butylphosphine was a milestone in this area. The contributions of Hartwig, Buchwald and Nolan are also important along with the original contributions of Stille, Migita, Heck, Suzuki, Kumada, Sonogashira and Hiyama. The coupling chemistry is still dominated by Pd, although base metals such as Ni, Cu, Co, Fe etc., are showing some success in this area. Our role along with many academic groups is to make these technologies available to the fine chemical and pharmaceutical industries by developing novel pre-formed, air stable, highly active and commercially available catalysts and demonstrating their applications in organic synthesis.

## 4.7.1 Suzuki Coupling

In the last two decades, the development of new and highly active catalysts by various academic and industrial groups has dramatically increased the scope and commercial viability of organic synthesis *via* Pd catalyzed carbon-carbon coupling. Powerful coupling methodologies, such as Heck, Suzuki, Sonogashira, Negishi, Tsuji-Trost and Buchwald-Hartwig coupling, enable synthetic organic chemists to accelerate total syntheses of API's *via* carbon-carbon coupling.[1] Among the various name reactions in C-C coupling, Suzuki coupling has become the most practiced reaction in industry as evidenced by a recent literature search.[2]

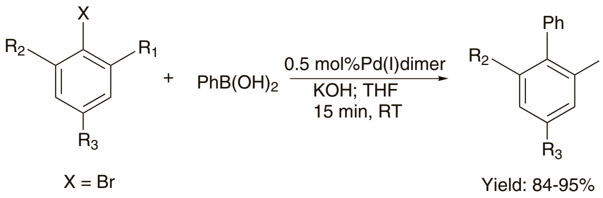
As shown in Scheme 1 below the choices of the ligand, metal, base and solvent are important in determining the oxidative addition, transmetallation and reductive elimination steps.



**Scheme 1.** Proposed mechanism for Suzuki coupling.

Suzuki first reported the use of Pd for the coupling of an aryl boronic acid and an aryl halide to prepare biaryl compounds in 1981.[3] Since this discovery, various modifications of the reaction conditions have been made which have increased the scope of this reaction.[4] A major breakthrough has been the discovery of new catalysts for challenging substrates such as unactivated aryl bromides and aryl chlorides. Of particular note is Fu's work on the use of Pd-based $t$-Bu$_3$P complexes. Fu's work in this area, along with Koie's original work on amination, showed that $t$-Bu$_3$P, in conjunction with a Pd catalyst precursor, is a very good system for aryl chloride coupling chemistry.[5] Subsequently, Hartwig[6], Buchwald,[7] Li,[8] Guram,[9] Beller[10] and Reetz[11] applied a similar concept: the use of a bulky electron-rich organophosphine to accomplish similar challenging transformations, involving unactivated aryl halides.

The use of air-stable, active catalysts is a preferred choice for many pharmaceutical and fine chemical companies. Although $t$-Bu$_3$P is a very active ligand for challenging coupling reactions, this pyrophoric, low melting solid requires special and careful handling techniques. The utilization of the known, fully formed Pd complexes of $t$-Bu$_3$P such as Pd($t$-Bu$_3$P)$_2$ , **Pd-116®** and [Pd($\mu$-Br)$t$-Bu$_3$P]$_2$, **Pd-113** to circumvent some of these problems was recently demonstrated by Fu and Hartwig respectively. Johnson Matthey has developed economical and novel commercial routes for these two catalysts in excellent purities. These types of catalysts are extremely active in a range of C-C coupling reactions, but do suffer from handling and storage issues. However, they are not more difficult to handle than the well-known Pd(PPh$_3$)$_4$, if synthesized in pure crystalline form. **Pd-113** is a very good catalyst for room temperature Suzuki coupling.[12]



**Scheme 2.** Room temperature Suzuki coupling of sterically bulky aryl bromides

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[1] (a) Diederich, F.; Stang, P.J. (eds) *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH Weinheim, **1998.** (b) Suzuki, A. *J. Organomet. Chem.* 1999, **576**, 147. (c) Colacot, T. *Platinum Metals Rev.* **2001**, *45*, 22. (d) de Meijere, A.; Diederich, F (eds) *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH, Weinheim 2 nd ed., **2004**. (e) Miura M., *Angew. Chem. Int. Ed.*. **2004**, *43*, 2201. (f) Corbet, J.P., Mignani G. *Chem Rev* 2006, **106,** 2651.

[2] Suzuki Coupling Publications/ (Patents): 2000-2007 ~3300/ (415) 1990-1999 ~3500/ (16) ; 1980-1989 ~2 / (0).

[3] Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.*, **1981**, *11*, 513.

[4] Miyaura, N.; Suzuki, A. *Chem. Rev.*, **1995**, *95*, 2457.

[5] (a) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2287; (b) Littke, A.F.; Dai, C.; Fu, G.C. *J. Am. Chem. Soc.*, **2000**, *122*, 4020; (c) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.*, **1998**, *39*, 617.

[6] Hamann, B. C.; Hartwig, J.F. *J. Am. Chem. Soc.*, **1998**, *120*, 7369.

[7] Old, D. W.; Wolfe, J.P.; Buchwald, S.L. *J. Am. Chem. Soc*, **1998**, *120*, 9722.

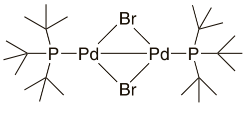
[8] Li, G.Y.; Zheng, G.; Noonan, A.F. *J. Org. Chem.*, **2001**, *66*, 8677.

[9] Bei, X.; Turner, H.W.; Weinberg,W.H.; Guram, A.S. *J. Org. Chem.*, **1999**, *64*, 6797.

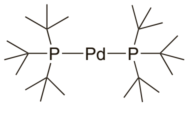
[10] Zaft, A.; Ehrentraut, A.; Beller, M. *Angew. Chem. Int. Ed*, **2000**, *39*, 4153.

[11] Reetz, M.T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed.*, **1998**, *37*, 481.

[12] (a) Stambuli, J.P.; Kuwano, R.; Hartwig, J.F.; *Angew. Chem., Int. Ed.*, **2003**, *41*, 4746. (b) Colacot, T.J.; *Platinum Metals Review*, **2009**, *53*, 183.



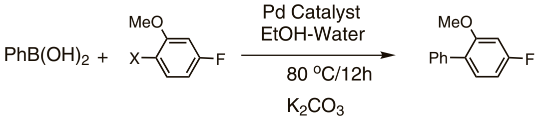
$[Pd(t\text{-}Bu_3P)Br]_2$ Pd-113



$[Pd(t\text{-}Bu_3P)_2]$ Pd-116

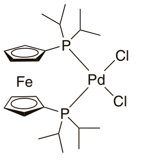
As part of Johnson Matthey's continued efforts to introduce new air-stable and active coupling catalysts, we reported[13] the synthesis of 1,1′-bis(di-isopropylphosphino)-ferrocene palladium dichloride $PdCl_2$(d*i*ppf), **Pd-119** and 1,1′-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride $PdCl_2$(d*t*bpf), **Pd-118**®, in addition to developing 1-1′-bis(di-cyclohexyl phosphino) ferrocene palladium dichloride, $PdCl_2$ (dcypf), **Pd-127**. These catalysts have been successfully shown to be highly active in Suzuki coupling reactions when compared to other commercial catalysts such as $PdCl_2$(dppf), $PdCl_2$(dppe), $PdCl_2(PPh_3)_2$, $PdCl_2(Cy_3P)_2$ and $PdCl_2$DPEPhos (Table 1)[13]. Johnson Matthey also has access to a sterically bulky mono-phosphine ligand, Q-Phos. Q-Phos is a high performance ligand for challenging cross-coupling processes including Suzuki reactions.[14]

**Table 1**. Comparison of the activities of Pd catalysts for a model Suzuki coupling reaction.

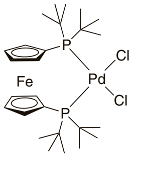


| entry | catalyst | X | loading (equiv) | yield (%) |
|---|---|---|---|---|
| 1 | $PdCl_2(Ph_3P)_2$ | Br | 0.01 | 93 |
| 2 | $PdCl_2(Cy_3P)_2$ | Br | 0.01 | 100 |
| 3 | $PdCl_2$(dppe) | Br | 0.01 | 100 |
| 4 | $PdCl_2(o\text{-}tol_3P)_2$ | Br | 0.01 | 100 |
| 5 | $PdCl_2$(dppf) | Br | 0.01 | 100 |
| 6 | $PdCl_2$(d*i*ppf) | Br | 0.01 | 100 |
| 7 | $PdCl_2(Ph_3P)_2$ | Cl | 0.01 | 2 |
| 8 | $PdCl_2(Cy_3P)_2$ | Cl | 0.01 | 2 |
| 9 | $PdCl_2$(dppe) | Cl | 0.01 | 5 |
| 10 | $PdCl_2$(dppf) | Cl | 0.01 | 4 |
| 11 | $PdCl_2(o\text{-}tol_3P)_2$ | Cl | 0.01 | 7 |
| 12 | $PdCl_2$(DPEPhos) | Cl | 0.01 | 2 |
| 13 | $PdCl_2$(d*i*ppf) | Cl | 0.01 | 9 |
| 14 | $PdCl_2$(d*t*bpf) | Cl | 0.01 | 65 |
| 15 | $PdCl_2$(d*t*bpf) | Cl | 0.01 | 100* |

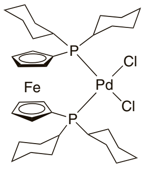
* All reactions were conducted in EtOH-water(1:1) at 80°C, except for entry 15, where DMF at 120°C was used.



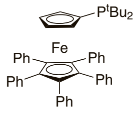
**$PdCl_2$(d*i*ppf) Pd-119**



**$PdCl_2$(d*t*bpf) Pd-118**



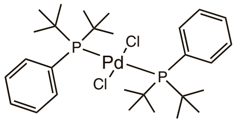
**$PdCl_2$(dcypf) Pd-127**



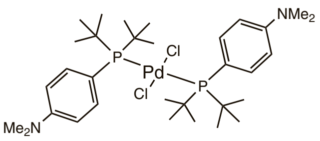
**Q-Phos**

Suzuki coupling applications of heterocyclic chlorides and aryl halides bearing free amine groups using air-stable catalysts have recently been reported using the catalysts $PdCl_2(t\text{-}Bu_2PAr)_2$ (Ar= Ph- [**Pd-122**], $Me_2NC_6H_5$- [**Pd-132**]).[15] These catalysts are commercially available through Johnson Matthey.

The applications of supported catalysts such as FibreCat® in Suzuki coupling of various aryl halides have also been demonstrated by us and others.[16]



**Pd-122**



**Pd-132**

As stated by Fu, "*there are a large number of parameters in a Suzuki reaction - palladium source, ligand, additive, solvent, temperature, etc.- and there are correspondingly, a large number of protocols for accomplishing the transformation, the choice of which depends on the structure of the reactants.*[17] Therefore, proper choice of the catalyst and reaction conditions are very important in accomplishing the desired transformation in good yield and selectivity. We investigate those parameters systematically, optimize the routes, in addition to developing new catalysts. These services are available to customers upon request.

[13] Colacot, T.; Shea, H. A. *Org. Lett.*, **2004**, *6*, 3731.

[14] Katao, N.; Shelby, Q.; Stambuli, J.P.; Hartwig, J.F. *J. Org. Chem.*, **2002**, *67*, 5553.

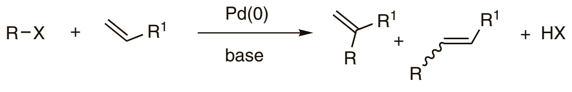
[15] Guram, A.S.; Allen, J.G.; Wang, X.; Schenkel, L.B.; Chan, J.; Bunel, E.E.; Faul, M.M.; Larsen, R.D.; Martinelli, M.J.; Reider, P.J. *Org. Lett*. **2006**, *8*, 1787.

[16] (a) Colacot, T.J.; Carole, W.A.; Neide, B.A; Harad, A. *Organomettallics* **2008**, *27*, 5605. (b) Colacot, T; Gore, E. S.; Kuber, A. *Organometallics* **2002**, *21*, 3301. (c) Wang, Y.; Sauer, D.R.; *Org. Lett.* **2004**, *6*, 2793. (d) Jiang, X.; Sclafani, J.; Prasad, K.; Repic, O.; Blacklock, T. J. *Org. Process Res. Dev.* **2007**, *11*, 769. (e) Colacot, T.J. Fibrecat in *Encyclopedia of Reagents for Organic Synthesis* [Online], John Wiley & Sons Ltd., www.mrw.interscience.wiley.com/eros **DOI: 10.1002/047084289X.rn00968**

[17] Littke, A.F.; Dai, C.; Fu, G.C. *J. Am. Chem. Soc.* **2000**, *122*, 4020 (see references 30 and 31 therein).

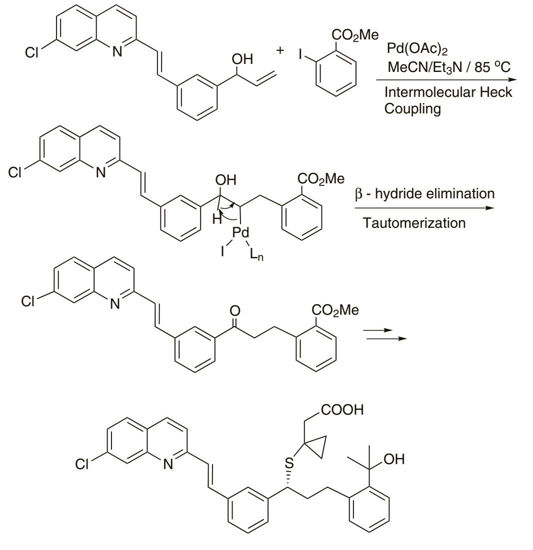
## 4.7.2 Heck Coupling

A Japanese scientist, Mizoroki (1971) and an American scientist, Heck (1972) developed independently a protocol to couple an aryl or alkenyl halide or pseudohalide with an olefin in the presence of a Pd based catalyst.



R = alkenyl, aryl
X = I, Br, Cl, OTf, OTs, COCl, COOH

The application of this chemistry includes the synthesis of hydrocarbons, conducting polymers, light emitting electrodes, dyes, and enantioselective synthesis of natural products. The Heck reaction has been used for large scale syntheses of pharmaceutical intermediates and is the key coupling step in the synthesis of Singulair,® Merck's treatment for asthma and allergies.[1, 2]



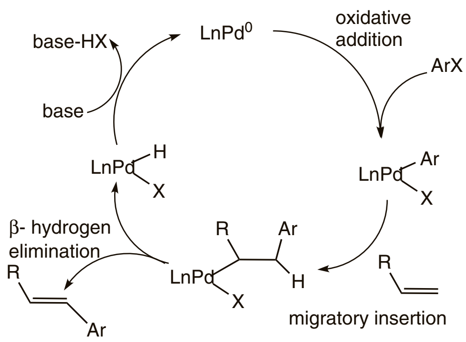
**Synthesis of Singulair® (Montelukast)**

The versatility of Heck-type reactions has been the source of a myriad of reaction conditions.[3] Typically, the metal of choice is Pd, which is commonly used as a homogeneous catalyst, with or without ligands.

The homogeneous Pd-catalysts without phosphine ligands are believed to proceed *via* ionic intermediates and generate very active catalytic species, usually in the presence of polar solvents (e.g. DMA). These conditions are known as the Jeffrey conditions.[4] However, the highly active species with an undefined coordination sphere may be affected by changes in reaction conditions (solvent, concentration) and each ligandless catalytic system has to be designed specifically for a particular reaction.[3] Therefore such systems are not practical.

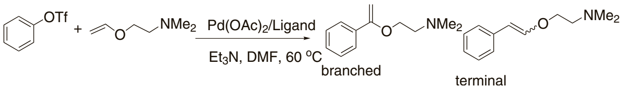
On the other hand, numerous well-defined Pd-phosphine pre-catalysts have been shown to be more reproducible and general with respect to variable reaction conditions.[3]

The Heck reaction product forms in the migratory insertion step of the catalytic cycle. The oxidation state of Pd during migratory insertion is +2. In this step the branch to linear selectivity *(regio)* as well as *cis* to *trans* selectivity (positional isomers) occurs, depending on the nature of the ligands and reaction conditions.



**Mechanism of Heck Coupling**

For instance, bulky bidentate phosphines with relatively larger bite angles generally give the branched product. For bidentate phosphine ligands with smaller bite angles a mixture of terminal and branched olefins is generated, while for monophosphines or ligandless systems, the terminal olefin product is generated predominantly.[5]



| ligand | branched | terminal |
|---|---|---|
| dppf | 99 | 1 |
| dppb | 77 | 23 |
| dppp | 99 | 1 |
| dppe | 83 | 17 |
| dppm | 1 | 99 |
| $Ph_3P$ | 1 | 99 |
| none | 1 | 99 |

1 Larsen, R. D.; Corley, E. G.; King, A. O.; Carroll, J. D.; Davis, P.; Verhoeven, T. R.; Reider, P. J.; Labelle, M.; Gauthier, J. Y.; Xiang, Y. B.; Zamboni, R. J. *J. Org. Chem.* **1996**, *61*, 3398.

2 King, A. O.; Corley, E. G.; Anderson, R. K.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J.; Xiang, Y. B.; Belley, M.; Leblanc, Y.; Labelle, M.; Prasit, P.; Zamboni, R. J. *J. Org. Chem.* **1993**, *58*, 3731.

3 Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.*, **2000**, *100*, 3009.

4 Jeffery, T. In *Advances in Metal-Organic Chemistry*; Liebeskind, L.S., Ed.; JAI Press: Greenwich, CT, 1996; 5, 153. See also: Ziegler, C. B., Jr.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941.

5 Larhed, M.; Andersson, C.-M.; Hallberg, A. *Tetrahedron* **1994**, *50*, 285.

In addition, substrates also play an important role in *regio-* and *stereo-* selectivity. For example, olefins containing electron withdrawing groups tend to form terminal products, while substrates with neutral and electron rich substituents favor mixed products under classical conditions (Figure 1).

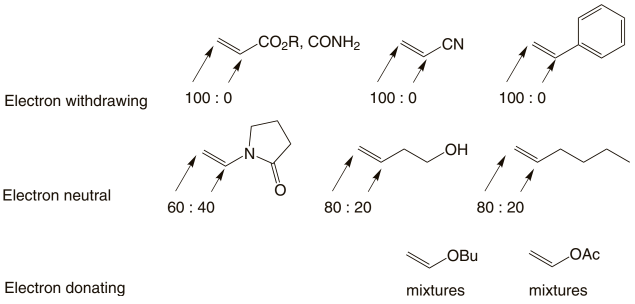
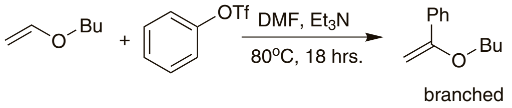


**Figure 1.** Effect of substrate on selectivity under classical conditions (Pd (OAc)$_2$ with Ph$_3$P in Et$_3$N base and DMF).

The reactions carried out under cationic conditions in the absence of halides or halide scavengers tend to increase the branch selectivity when electron donating substrates are used (Chart 1).



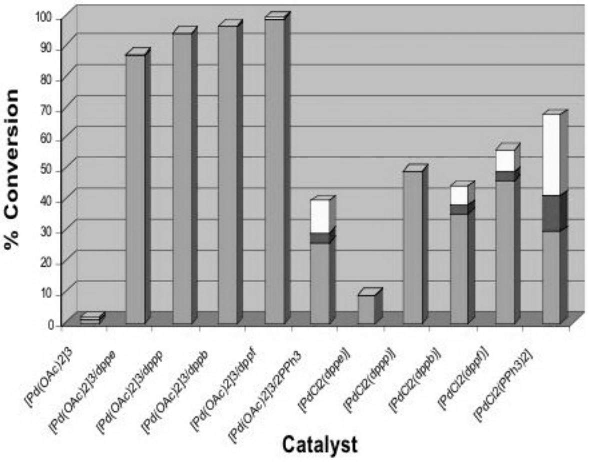
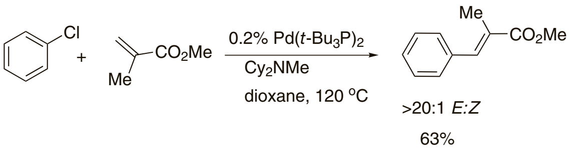
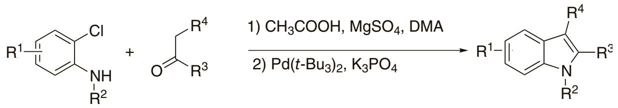


**Chart 1**. Catalyst effect on selectivity ( ▨ – branched, ☐ - *trans*, ■ - *cis*)

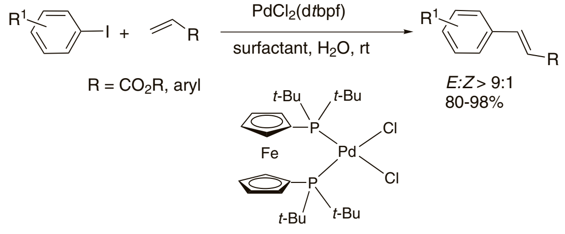
Heck coupling has been applied to challenging substrates such as *ortho* - substituted aryl chlorides with the aid of the Pd complexes of bulky electron rich phosphine ligands such as tri-*t*-butylphosphine (*t*-Bu$_3$P). The original conditions were developed by Fu, which included the use of Cs$_2$CO$_3$ base, although his subsequent work indicated that Cy$_2$NMe was also a very good base. His group also used KF base for room temperature coupling reactions. The scope of the substrate was extended to aryl and vinyl chlorides, which react with various olefins under mild conditions in the presence of low catalyst loadings of Pd(*t*-Bu$_3$P)$_2$, **Pd-116**®.[6]



Pd(*t*-Bu$_3$P)$_2$ can be also used for indole and azaindole syntheses by direct annulation.[7] In the following example, *in situ* enamine formation followed by intramolecular Heck coupling of the enamine with aryl chlorides generates various indoles and azaindoles. This is a very practical route for *regioselective* indole synthesis.



Hartwig *et al.* have identified both Pd-*t*-Bu$_3$P and Pd-d*t*bpf (d*t*bpf = (1,1'-bis(di-*t*-butylphosphinoferrocene)) as the best catalyst systems for the olefination of unactivated aryl chlorides,[8] while Lipshutz *et al.* have developed a protocol in which aryl iodides are olefinated at room temperature using water as the only solvent in the presence of a surfactant using PdCl$_2$(d*t*bpf), **Pd-118**® catalyst.[9]



PdCl$_2$(d*t*bpf) **Pd-118**

Over the past two decades, the catalytic asymmetric Heck reaction has been developed as an efficient method to create chiral tertiary and quaternary carbon centers enantioselectively through carbon-carbon bond formation.[10] The asymmetric variant of the Heck reaction has been extensively applied in the syntheses of natural products such as terpenoids, alkaloids, polyketides, etc.

[6] a) Littke, A.F.; Fu, G. C. *J. Am. Chem. Soc.*, 2001, *123*, 6989. b) Littke, A. F.; Fu, G. C *J. Org. Chem.*, **1999**, *64*, 10.

[7] Nazare, M.; Schneider, C.; Lindenschmidt, A.; William Will, D. *Angew. Chem. Int. Ed.*, **2004**, *43*, 4526.

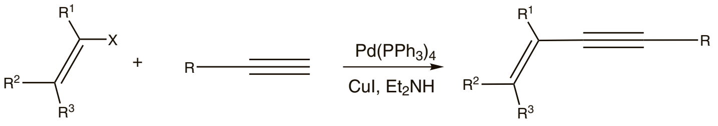
[8] Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123.

[9] Lipshutz, B. H.; Taft, B. R. *Org. Lett.*, **2008**, *10*,1329.

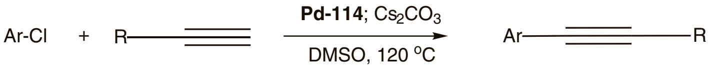
[10] Dounay, A. B.; Overman, L. E. *Chem. Rev.*, **2003**, *103*, 2945.

## 4.7.3 Sonogashira Coupling

The classical Sonogashira reaction involves the coupling of terminal alkynes with aryl or vinyl halides (mostly iodides) in presence of a palladium catalyst with a copper(I) cocatalyst, and an amine base.[1] Typically, the reaction requires anhydrous and anaerobic conditions, but newer procedures have been developed where these restrictions may not be important.[2] The basic mechanism is very similar to the standard coupling, where Cu is responsible for activating the alkyne. Homocoupling of the alkyne can be a major problem in Sonogashira coupling.

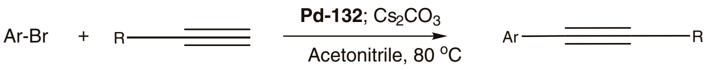


Cu-free Sonogashira reactions have been demonstrated successfully by using $(Cy_3P)_2PdCl_2$, **Pd-114**.[3] Inorganic bases instead of organic amines can also be used.



Buchwald has found that Cu inhibits the coupling reaction in certain cases, especially in Ar-Cl coupling.[4]

Recently, we found that $[(Me_2N\text{-}C_6H_5)P(t\text{-}Bu)_2]_2PdCl_2$, **Pd-132** catalyst is a very efficient catalytic system for Cu-free Sonogashira coupling at low catalyst loading and under relatively mild reaction temperatures with aryl bromide substrates.[5] This catalyst was superior to **Pd-114**.



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[1] (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.*, ***1975***, 4467. (b) Rossi, R; Carpita, A.; Bellina, F. *Org. Prep. Proceed. Int.*, ***1995***, *27*, 129.
[2] Liang, B.; Dai, M. ; Chen, J.; Yang, Z. *J. Org. Chem.*, **2005**, *70*, 391.
[3] Yi, C.; Hua, R. *J. Org. Chem.*, **2006**, *71*, 2535.
[4] Gelman, D.; Buchwald, S.L. *Angew. Chem. Int. Ed.*, **2003**, *42*, 5993.
[5] Li H.; Colacot, T. Manuscript under preparation.

## 4.7.4 Cross-Coupling with Organometallic Reagents

The use of aryl-, alkenyl-, or alkyl- metal complexes as coupling partners containing metals or metalloids such as magnesium, zinc, tin, or silicon has been getting a lot of interest recently, although the chemistry has been discovered several decades ago. Generally, the use of various organometallic reagents as coupling partners is highly dependent on the nature of the substrate and reaction conditions.[1, 2]

$$R\text{-}X + R'\text{-}MY_n \xrightarrow{\text{Pd catalyst}} R{-}R' + MXY_n$$

R, R' = aryl, alkenyl, alkyl

M = Mg: Kumada
M = Zn, Zr: Negishi
M = Sn: Stille
M = Si*: Hiyama
* Si is a metalloid

These organometallic reagents can facilitate the transmetallation step after the oxidative addition step in the catalytic cycle. Subsequently, the product formed through reductive elimination results in carbon-carbon bond formation. One important feature of these reactions is that the use of base is not required.

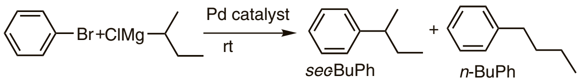
### a. Kumada Coupling

Kumada followed by Corriu, Hayashi and Tamao were able to use Grignard reagents as the nucleophilic coupling partners in cross coupling chemistry. Although the earlier work included the use of Ni-based homogeneous catalysts, Kumada coupling has continually developed using palladium catalysts. Often, Pd-based catalysts are preferred over Ni-based catalysts due to their lower toxicity, and higher activity and selectivity, although Ni complements Pd in several cases.

Kumada Coupling can be used for both $C(sp^2) - C(sp^2)$ and $C(sp^3) - C(sp^2)$ coupling. The type of ligand used (e.g. monodenate *vs* bidentate) is also very important in achieving high activity and selectivity. For example, $PdCl_2(dppf)$, **Pd-106** was demonstrated to be a very selective and active catalyst for the coupling of *sec*-butylmagnesium chloride with aryl bromides.[1, 3]

---

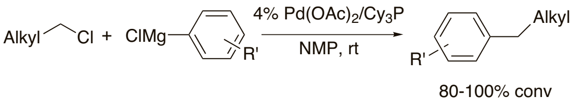
[1] Corbet, J.-P.; Mignani, G. *Chem. Rev.*, **2006**, *106*, 2651.
[2] Colacot, T.J. *Platinum Metals Rev.*, **2008**, *52*, 172.
[3] Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.*, **1984**, *106*, 158.



| catalyst | time (h) | bite Angle (º) | ***sec*-BuPh** (%) | ***n*-BuPh** (%) |
|---|---|---|---|---|
| $PdCl_2(Ph_3P)_2$ | 24 | n/a | 5 | 6 |
| $PdCl_2$(dppe) | 48 | 85.8 | 0 | 0 |
| $PdCl_2$(dppp) | 24 | 90.6 | 43 | 19 |
| $PdCl_2$(dppb) | 8 | 94.51 | 51 | 25 |
| $PdCl_2$(dppf) | 1 | 99.07 | 95 | 2 |
| $NiCl_2(Ph_3P)_2$ | 23 | n/a | 3 | 5 |

Grignard reagents have several advantages: their synthesis is well understood at pilot and plant scale, they allow mild reaction conditions in the presence of Ni or Pd-based catalysts, they provide good selectivity and reaction productivity. Due to these advantages, Kumada reaction has recently been used for applications such as syntheses of unsymmetrical biaryls and styrene derivatives.[4]

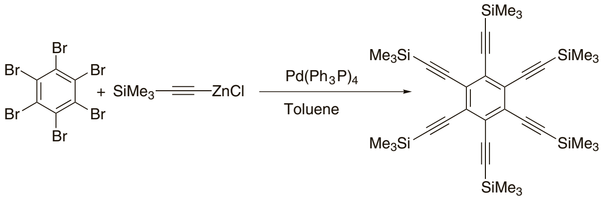
With recent advances in the area of Pd-catalyzed coupling using organomagnesium compounds the aryl Grignard has also been used for C($sp^3$) -C($sp^2$) bond formation. Efficient coupling of alkyl halides with various aryl Grignard reagents were achieved by using a $Pd(OAc)_2/Cy_3P$ catalyst system.[5]



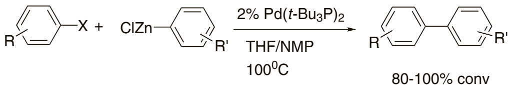
## b. Negishi Coupling

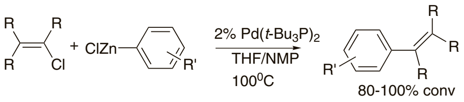
The Pd-catalyzed cross coupling of organozinc reagents with various aryl halides and pseudohalides has been pioneered by Negishi, hence this reaction is known today as Negishi Coupling. Most organozinc reagents can be prepared either in advance or *in situ* by the reaction of organomagnesium, organolithium, or organoaluminium compounds with a zinc halide. Although less reactive than their organomagnesium counterparts, organozinc reagents present the advantage of having a wide range of functional group tolerance (e.g. inertness to ketones, esters, amines, nitriles, nitro compounds, etc).

The versatility of the Negishi reaction derives from the ability of various organozinc reagents (alkyl, alkenyl, alkynyl, aryl) to couple with different organohalide electrophiles (alkyl, alkenyl, alkynyl, aryl).[1,6] For instance, polyethynyl derivatives have been synthesized by using $Pd(Ph_3P)_4$, **Pd-101**-catalyzed reaction of hexabromobenzene with ethynylzinc halide. The synthesis of substituted alkynes through alkynylation using alkynyl zinc halides represents an efficient alternative to the Sonogashira and Castro-Stephens reactions, which employ copper as an additive.



Other aryl, allyl, benzyl, propargyl, and alkyl organozinc reagents have been employed successfully in Pd-catalyzed couplings with various electrophiles. For example, Fu et al. had utilized Pd(*t*-$Bu_3P)_2$, **Pd-116®** to develop a general Negishi protocol for the coupling of aryl and vinyl chlorides. Advantages of this method are mild reaction conditions, greater functional group tolerance and extension to heteroaryl halides.[7]





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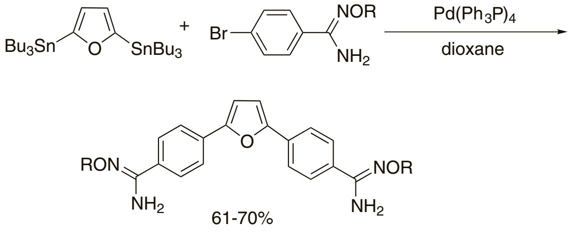
[4] Hassan, J.; Svignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.*, **2002**, *102*, 1359.
[5] Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. Angew. *Chem. Int. Ed.*, **2002**, *41*, 4056.
[6] Negishi,, E.; Anastasia, L. *Chem. Rev.*, **2003**, *103*, 1979.
[7] Dai, C.; Fu, G. C. *J. Am. Chem. Soc.*, **2001**, *123,* 2719.

## c. Stille Coupling

Kosugi-Migita-Stille reaction is a very versatile Pd-catalyzed transformation, which allows the formation of C-C bonds from a variety of organohalides or pseudohalides with organostannanes. Despite their toxicity, organostannanes are still widely used due to their stability, compatibility with various functional groups as well as versatility to form products from a diverse combination of organohalides and organostannanes.

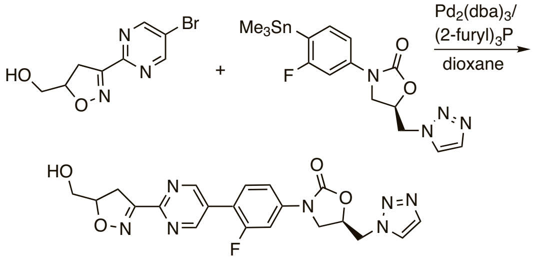
$$R\text{-}X + R^1SnR_3 \xrightarrow{\text{Pd catalyst}} R{-}R^1 + XSnR_3$$

When organostannanes are used as the nucleophilic coupling partners, Pd is the metal of choice. Triphenyl phosphine is typically the ligand of choice. For instance, $Pd(Ph_3P)_4$, **Pd-101** was used to synthesize the prodrug furamidine, which was used against Pneumocystitis carinii pneumonia and human African trypansomiasis.[1]



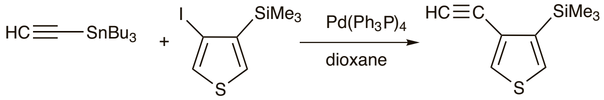
Synthesis of Furamidine

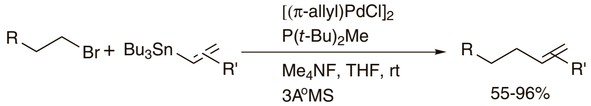
Less electron rich ligands such as tri-2-furylphosphine, $(2\text{-furyl})_3P$ and $AsPh_3$ seem to accelerate the transmetallation step, which is believed to be the rate determining step. $Pd_2(dba)_3$ in combination with $(2\text{-furyl})_3P$ was used by AstraZeneca in the synthesis of antibacterial oxazolidinone derivatives.[2]



Synthesis of an Antibacterial Agent

Alkynylation of various electrophiles using alkynyl tin reagents has also been used as an alternative method to Sonogashira reaction to prepare various substituted alkynes, while functionalized alkyl halides could be coupled at rt with various alkenyl tin reagents.[3]





## d. Hiyama / Hiyama – Denmark Coupling

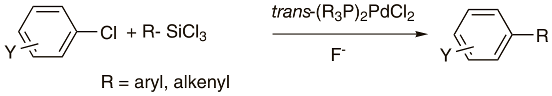
The use of organsilicon compounds as coupling partners has been very attractive due to their wide availability, diversity, stability, low toxicity as well as high tolerance to various reaction conditions. Due to their lower activity, organosilicon reagents have to be activated to their corresponding hypervalent Si(V) species in order to be able to participate in the transmetallation step. Usually, stoichiometric amounts of fluoride-base additives are used. Generally, Hiyama coupling is performed using unsophisticated Pd-based catalysts. For instance, Hiyama reported the coupling of vinyl, ethynyl, and allylsilanes with organohalides (aryl, vinyl, allyl) to take place in the presence of a simple Pd-catalyst, $[(\pi\text{-allyl})PdCl]_2$, **Pd-110**.[4]

1 Boykin, D. W.; Anbazhagan, M.; Tidwell, R.; R. WO 2004051217 A2, 2004.
2 Gravestock, M. B.; Hales, N. J.; Huynh, H. K. WO 2004056817 A1, 2004.
3 Menzel, K.; Fu, G.C. *J. Am. Chem. Soc.*, **2003**, *125*, 3718.
4 Yasuo Hatanaka,Y.;Hiyama, T. *J. Org. Chem.*, **1988**, *53*, 918.

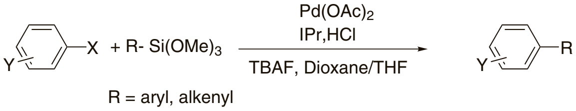
$$R^1-X \ + R^2\text{- }SiMe_3 \xrightarrow[F^-]{[(\pi\text{-allyl})PdCl]_2} R^1-R^2$$

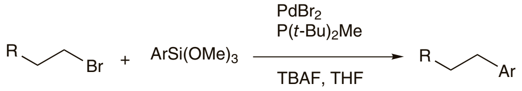
$R^1$ = aryl, alkenyl, allyl
$R^2$ = alkenyl, allyl, alkynyl

Aryl and alkenyl chlorosilanes can also be used as coupling partners with activated aryl chlorides, when *trans*-$(R_3P)_2PdCl_2$ catalysts are used.[5]

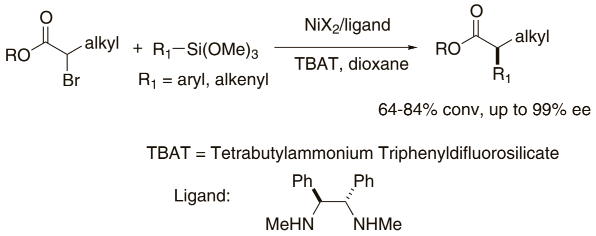


The reaction rates may be enhanced when the alkyl group is replaced with an alkoxy group, which in combination with electron rich ligands can facilitate the coupling reaction of unactivated aryl chlorides[6] or primary alkyl bromides.[7]



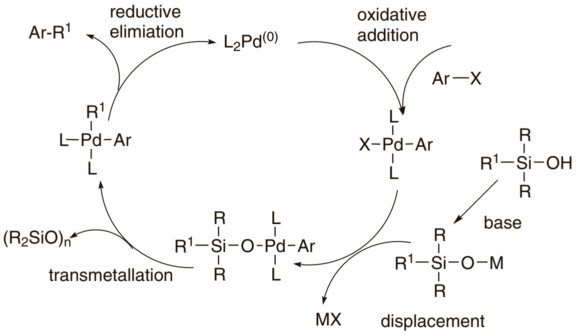


Fu *et al*. have also developed a Ni/chiral diamine - catalyzed enantioselective variant of Hiyama reaction, when racemic -α-bromoesters are coupled with trimethoxysilane compounds to generate chiral α-substituted esters.[8]



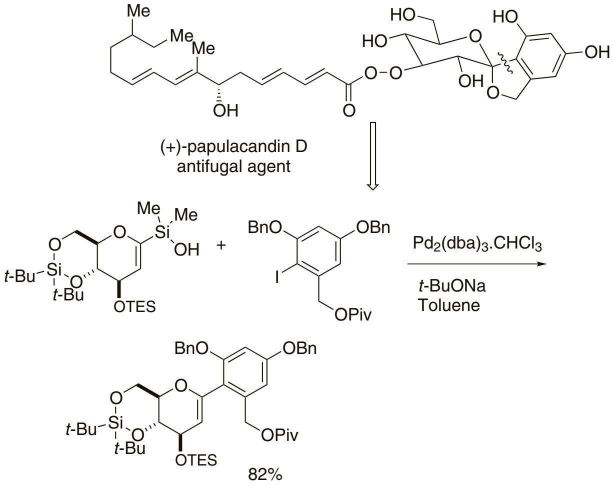
TBAT = Tetrabutylammonium Triphenyldifluorosilicate

Organosilanols are also efficient nucleophilic coupling partners for the cross coupling reactions, again, without the need to be activated by a fluoride base. The fluoride-free conditions have been developed by Denmark *et al.* and the reaction is often called the Hiyama-Denmark coupling. Therefore, substrates bearing silyl-protecting groups can be now employed in this cross coupling reaction.[9] Organosilanols are deprotonated using different protocols. The resulting silanolate species binds covalently to the palladium center, forming a complex that facilitates the transmetallation step. Through X-ray structure determination Denmark *et al.* demonstrated the existence of the Pd-O-Si species and that, in this case, the generation of hypervalent Si species is not necessary.[9]



**Denmark's Proposed Mechanism**

This methodology affords the practical formation of C-C bonds by coupling various aryl, heteroaryl, alkenyl and alkynyl silanols with aryl and alkenyl halides in the presence of inorganic bases and Pd-catalysts such as $Pd(dba)_2$, **Pd-93**, $Pd_2(dba)_3.CHCl_3$, **Pd-95**, $[(\pi\text{-allyl})PdCl]_2$, **Pd-110**, or $Pd(t\text{-}Bu_3P)_2$, **Pd-116®**, and has found applications in the synthesis of pharmaceutical ingredients.



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[5] Ken-ichi Gouda, K.; Hagiwara, E.; Hatanaka, Y.; Hiyama, T. *J. Org. Chem.*, **1996**, *61*, 7232.
[6] Lee, H.-M.; Nolan, S.P. *Org. Lett.*, **2000**, *2*, 2053.
[7] Lee, J.-Y.; Fu, G.C. *J. Am. Chem. Soc.*, **2003**, *125*, 5616.
[8] Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.*, **2008**, *130*, 3302.
[9] Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.*, **2008**, *41*, 1486.

# 4.7.5 FibreCat®

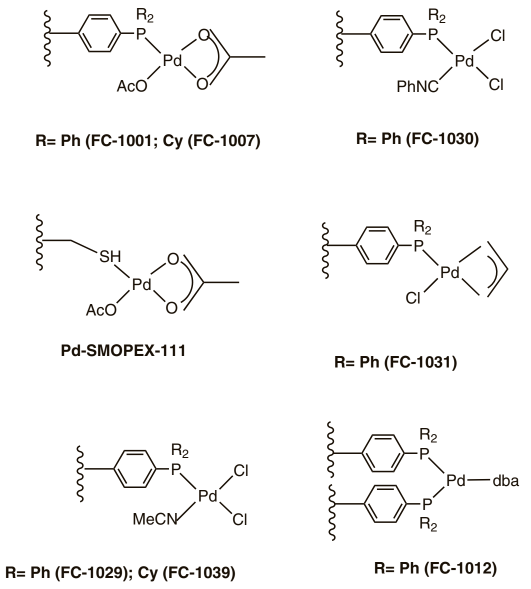
## Comparison of FibreCat® (Anchored) with Homogeneous Catalysts:

### FibreCat Palladium Series (1000) in Cross-coupling Reactions

The use of palladium in homogeneous catalysts for cross coupling reactions is steadily increasing in pharmaceutical processes. However, there remains concern over potential palladium contamination of the product. To address these concerns, Johnson Matthey has developed a new line of tunable, polymer supported palladium complexes of electron rich and bulky monodentate and bidentate ligands that provides ease of separation, good selectivity/ recyclability and no metal leaching.

The Palladium FibreCat series was developed specifically for C-C coupling reactions. The design of these catalysts allow for them to be tuned in three ways:

i) changing the palladium precursors
ii) changing the ligand on the support
iii) changing the ligand on the metal


R= Ph (FC-1001; Cy (FC-1007)

R= Ph (FC-1030)

Pd-SMOPEX-111

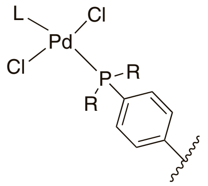
R= Ph (FC-1031)

R= Ph (FC-1029); Cy (FC-1039)

R= Ph (FC-1012)

**Figure 1.** First generation FibreCat for routine substrates (Ar-I and Ar-Br)

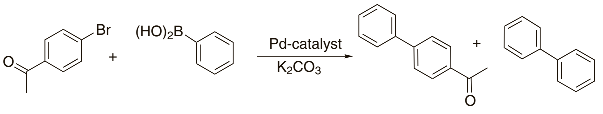
**Table 1.** New FibreCats developed for applications in Suzuki coupling of unactivated aryl halides



| R | L | % Pd | code | color |
|---|---|---|---|---|
| Ph | *t*-Bu$_3$P | 4.47 | FC-1032 | yellow |
| | Q-Phos | 6.34 | FC-1033 | brown |
| | PhP(*t*-Bu)$_2$ | 4.62 | FC-1034 | orange |
| | dppf | 4.64 | FC-1035 | orange |
| | BINAP | 4.85 | FC-1036 | orange |
| | dippf | 5.23 | FC-1037 | red |
| | (Me$_2$NC$_6$H$_4$)P(*t*-Bu)$_2$ | 4.37 | FC-1034A | gold |
| Cy | MeCN | 9.61 | FC-1039 | red |
| | *t*-Bu$_3$P | 5.76 | FC-1042 | gold |
| | Q-Phos | 6.61 | FC-1043 | brown |
| | PhP(*t*-Bu)$_2$ | 6.48 | FC-1044 | gold |
| | dppf | 5.61 | FC-1045 | gold |
| | BINAP | 6.63 | FC-1046 | gold |
| | dippf | 7.47 | FC-1047 | red |
| | (Me$_2$NC$_6$H$_4$)P(*t*-Bu)$_2$ | 4.33 | FC-1048 | gold |

### Suzuki & Heck Coupling of Aryl Bromides

The first generation of Pd-FibreCats have proven to be effective in the coupling of a variety of aryl bromides, with FC-1012 and FC-1029 being most efficient in terms of activity and selectivity towards the synthesis of unsymmetrical biaryl compounds. Recycling experiments revealed no or minimal Pd leaching in the Suzuki reaction involving simple aryl bromides.[1]



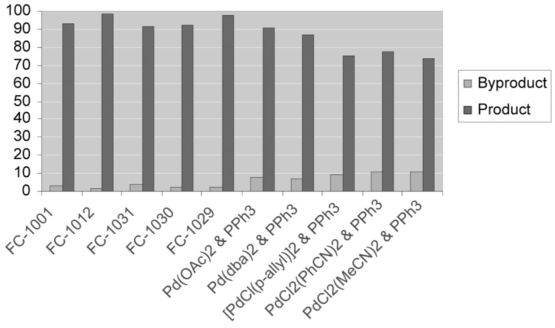


**Chart 1.** Comparison of FibreCats against their respective homogeneous systems

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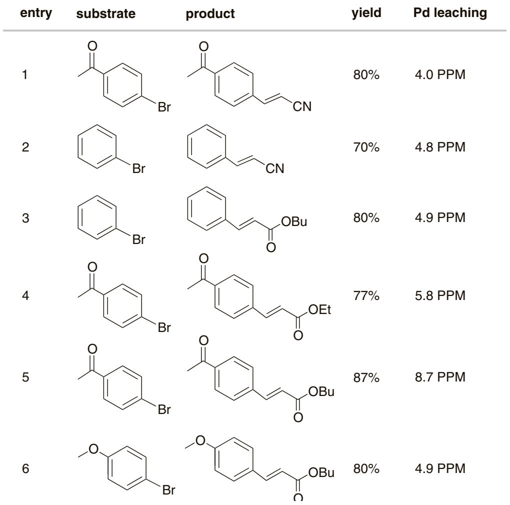
[1] Colacot,T. J.; Gore, E. S.; Kuber, A. *Organometallics* **2002**, *21*, 3301.

Similarly, the simple Pd-SMOPEX-111 (thiol grafted Smopex® treated with $Pd(OAc)_2$) was also employed in the Heck (Table 2) and Suzuki couplings of simple aryl bromides to give moderate to high conversions during four recycling trials with minimal Pd-leaching.[2]

**Table 2.** Pd-SMOPEX-111 in Heck coupling of aryl bromides



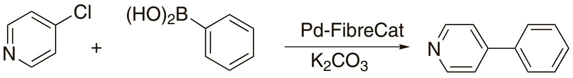
| entry | substrate | product | yield | Pd leaching |
|---|---|---|---|---|
| 1 |  |  | 80% | 4.0 PPM |
| 2 |  |  | 70% | 4.8 PPM |
| 3 |  |  | 80% | 4.9 PPM |
| 4 |  |  | 77% | 5.8 PPM |
| 5 |  |  | 87% | 8.7 PPM |
| 6 |  |  | 80% | 4.9 PPM |

## Suzuki Coupling of Aryl Chlorides

To our knowledge there are not many examples of supported catalysts available for Suzuki coupling of aryl chlorides. For challenging substrates, such as electron-rich aryl bromides and chlorides, the first generation of Pd-FibreCats was tuned in such a way to induce more electron density and steric bulk onto the Pd.

These second generation Pd-FibreCats were tested in the Suzuki cross coupling of 4-chloropyridine with phenylboronic acid. The $t\text{-}Bu_3P$ and $PhP(t\text{-}Bu)_2$- based FibreCat catalysts (FC-1042 and FC-1034, respectively) gave quantitative conversions to the coupled product.[3]

**Table 3.** Effectiveness of second generation FibreCats in comparison to first generation catalysts.

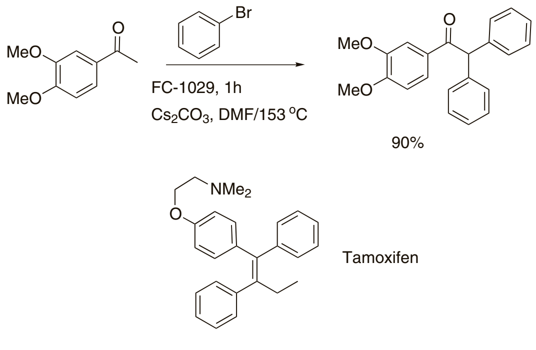


| catalyst | entry | loading | time | yield* |
|---|---|---|---|---|
| FC-1032 | 1 | 2 mol% | 8 | 11 |
|  | 2 | 3 mol% | 15 | 70 |
| FC-1039 | 3 | 2 mol% | 8 | 25 |
|  | 4 | 3 mol% | 15 | 36 |
| **FC-1042** | 5 | 2 mol% | 8 | 41 |
|  | 6 | 3 mol% | 15 | 100 (93) |
| FC-1029 | 7 | 2 mol% | 8 | 16 |
|  | 8 | 3 mol% | 15 | 16 |
| Pd-Smopex-111 | 9 | 2 mol% | 8 | — |
|  | 10 | 3 mol% | 15 | 6 |
| **FC-1034A** | 11 | 2 mol% | 8 | 59 |
|  | 12 | 3 mol% | 15 | 100 (92) |
|  | 13 [a] | 3 mol% | 4 | 100(94) |

*isolated yield [a] KF was used as base

## α-Arylation of Aryl Bromides

FibreCat 1007 and 1029 were reported for the selective mono- and diarylation of ketones.[4] The arylated products were isolated in very good yield and selectivity. The α,α-diarylated products from acetophenone, resemble *Tamoxifen*, an adjuvant drug used for the treatment of estrogen receptor-positive breast cancer.[4]



**Diarylation of ketones using FibreCat 1029**

## Leaching and Recyclability

An ideal supported homogeneous catalyst should demonstrate its application for higher activity without undergoing any leaching and therefore give very good recyclablilty. Johnson Matthey has performed several studies in this area. Some of the findings are summarized in the subsequent tables. There are also reports available on the reusability of FC-1029 up to five times in the α-arylation of ketones.[4] Studies performed by Novartis on Pd-SMOPEX-111 demonstrated it to be a recyclable catalyst, based on the results on Suzuki coupling of *p*-bormoacetophenone with phenylboronic acid.[2]

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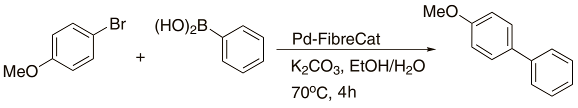
2 Jiang, X.; Sclafani, J.; Prasad, K.; Repic, O.; Blacklock, T. J. *Org. Proc. Res. Dev.,* **2007**, *11*, 769.

3 (a) Colacot, T. J.; Carole, W.A.; Neide, B. A.; Harad, A. *Organometallics*, **2008**, **27**, 5605. (b) Colacot, T.J., *Topics in Catalysis*, **2008**, *48*, 91. (c) Encyclopedia of Reagents for Organic Synthesis. DOI: 10.1002/047084289X.rn00968, John Wiley & Sons. Ltd., www.mrw.interscience.wiley.com/eros/, March 15, 2009, T. Colacot.

4 Churruca, F.; SanMartin, R.; Tellitu, I.; Dominguez, E. *Tet. Lett,* **2003,** *44*, 5925. (see reference therein)

Table 4. Comparison of various FIbreCats demonstrating different activity and leaching in Suzuki coupling

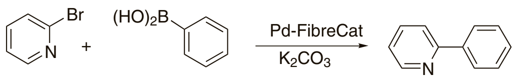


| entry | catalyst | loading | cycle | yield* | leaching |
|---|---|---|---|---|---|
| 1 | 1032 | 1 mol% | 1 | 100 (94) | <1.0 PPM |
| | | | 2 | 100 (92) | <1.0 PPM |
| | | | 3 | 100 (93) | 5.0 PPM |
| | | | 4 | 95 (87) | 10.00 PPM |
| 2 | 1039 | 0.5 mol% | 1 | 100 (93) | <1.0 PPM |
| | | | 2 | 98 (91, 5) | <1.0 PPM |
| | | | 3 | 94 (88) | 1.0 PPM |
| | | | 4 | 16 | 20.00 PPM |
| 3 | 1029 | 0.5 mol% | 1 | 100 (94) | 0.0 PPM |
| | | | 2 | 100 (91) | <1.0 PPM |
| | | | 3 | 92 (88) | 1.0 PPM |
| | | | 4 | 26 | 30.00 PPM |
| 4 | Pd Smopex-111 | 1 mol% | 1 | 100 (92) | <1.0 PPM |
| | | | 2 | 100 (91) | <1.0 PPM |
| | | | 3 | 77 (65) | 1.0 PPM |
| | | | 4 | 5 | 65.00 PPM |

*isolated yields

We have also tested substrates including heterocyclic bromides for recylability in Suzuki coupling reactions. For example, FC1034A gives better recyclability in comparison to FC-1032 and FC-1042 as shown below for 2-bromo pyridine system.[3a]

**Table 5.** Superior performance of FC-1034A



| catalyst | loading | cycle | yield* | leaching |
|---|---|---|---|---|
| FC-1032 | 3 mol% | 1 | 100 (92) | <1 ppm |
| | | 2 | 90(82) | <1 ppm |
| | | 3 | 60 | <1 ppm |
| | | 4 | 58 | <1 ppm |
| FC-1042 | 3 mol% | 1 | 100 (92) | <1 ppm |
| | | 2 | 100 (94) | <1 ppm |
| | | 3 | 91 (82) | <1 ppm |
| | | 4 | 82 | <1 ppm |
| FC-1034A | 3 mol% | 1 | 100 (94) | <1 ppm |
| | | 2 | 100(91) | <1 ppm |
| | | 3 | 100 (91) | <1 ppm |
| | | 4 | 96 (88) | <1 ppm |

*isolated yield

## Summary

The Pd-FibreCat family is a unique class of polymer-supported systems useful for various coupling reactions. This is a cost effective process technology, especially for aryl bromides. The ability to tune FibreCat in different ways makes it a very practical catalyst system for various substrates. In many cases, Pd leaching is within the acceptable range for API manufacture even under relatively drastic conditions and irrespective of the number of reuses. However, reaction conditions, choice of catalysts and the nature of the substrate may have a profound influence on leaching and life cycle of the catalyst. Several of these catalysts are being used in multi-kilo processes.

# 4.7.6 α-ARYLATION

Over the last decade, Pd-catalyzed α-arylation of carbonyl compounds has emerged as a new powerful C-C bond forming methodology. The groups of Hartwig[1] and Buchwald[2] have identified palladium precursors such as $Pd(OAc)_2$, **Pd-111** and $Pd_2dba_3$, **Pd-94** in conjunction with bulky, electron rich monodentate or bidentate phosphines as viable catalytic systems for such transformations. The α-arylation of ketones, amides, esters, nitriles and aldehydes can now be successfully carried out by a careful choice of catalyst, base and reaction conditions. For a comprehensive review of the developments made within this field, the reader is referred to recent literature articles.[3]

## Ketones

In 2004, Colacot and Shea reported the superior catalytic activity of an air-stable, preformed catalyst; $PdCl_2$(d*t*bpf), **Pd-118®** in Suzuki coupling of a wide variety of aryl chlorides.[4] Bidentate ferrocenylphosphine ligands have become a very important class of ligands in transition metal-catalyzed reactions in organic synthesis,[5,6] and the activity of **Pd-118®** was subsequently also investigated in the α-arylation reaction of ketones.[7]

A number of bis(phosphino)ferrocene based catalysts (Fig. 1) were employed in the arylation of propiophenone with 4-chlorotoluene, and both $PdCl_2$(d*t*bpf), **Pd 118®** and $PdBr_2$(d*t*bpf), **Pd-128** gave good conversions to the desired product (Table 1).

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[1] (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234 (see references therein). (b) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (c) Hamann, B. C.; Hartwig, J. F. **1997**, *119*, 12382. (d) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (c) Corbet, J.-P.; Mignani, G.; *Chem Rev* **2006**, *106*, 2651.

[2] (a) Palucki, M.; Buchwald, S.L. **1997**, *119*, 11108. (d) Nguyen, H. N.; Huang, X.; Buchwald, S.L. **2003**, *125*, 11818.

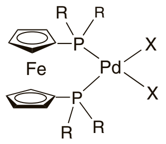
[3] (a) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem. Int. Ed.*, in press. (b) Bellina, F.; Rossi, R. *Chem. Rev.* **2009** ASAP.

[4] Colacot, T. J.; Shea, H. A. *Org. Lett.* **2004**, *6*, 3731.

[5] Togni, A.; Hayashi, T. *Ferrocenes*; VCH Verlagsgesellschaft, Weinheim, Germany 1995. (b) Stepnicka, P *From Materials and Chemistry to Biology* Wiley, Germany 2008.

[6] (a) Colacot, T. J.; Parisel, S. In *Ferrocenes: From Materials and Chemistry to Biology*, Wiley, Germany 2008. (b) Colacot, T. J. *Chem Rev.* **2003**, *103*, 3101 ( see references therein) (c) Colacot, T. J. *Platinum Met. Rev.* **2001**, *45*, 22 (d) Colacot, T. J.; Quian, H.; Cea-Olivares, R.; Hernandez-Ortega, S. *J. Organomet. Chem.* **2001**, 691, *637*.

[7] (a) Grasa, G. A.; Colacot, T. J. *Org. Lett.* **2007**, *9*, 5489.



R = Ph, X = Cl PdCl$_2$(dppf) **Pd-106**
R = $^i$*Pr*, X = Cl PdCl$_2$(dippf) **Pd-119**
R = Cy, X = Cl PdCl$_2$(dcpf) **Pd-127**
R = $^t$Bu, X = Cl PdCl$_2$(d*t*bpf) **Pd-118**
R = $^t$Bu, X = Br PdBr$_2$(d*t*bpf) **Pd-128**
R = $^t$Bu, X = I PdI$_2$(d*t*bpf) **Pd-138**

**Figure 1**. Bis(phosphino)ferrocene-PdX$_2$ complexes investigated in α-arylation reactions.

Interestingly, the *in situ* generated catalyst (by mixing Pd$_2$dba$_3$ with d*t*bpf) gave no activity under identical conditions. Surprisingly, PdI$_2$(d*t*bpf) gave only 12 % conversion, unlike in the case of the corresponding chloride and bromide, which gave 88-89 % conversion.

**Table 1.** Performance of Pd –bisphosphinoferrocene based catalysts in the arylation of propiophenone with 4-chlorotoluene.[a]

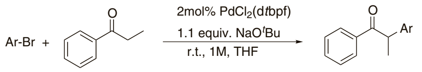
| entry | pre-catalyst | conv. (%)[b] |
|---|---|---|
| 1 | PdCl$_2$(dppf) | NR |
| 2 | PdCl$_2$(dippf) | 14 |
| 3 | PdCl$_2$(dcpf) | 42 |
| 4 | PdCl$_2$(d*t*bpf) | 88 |
| 5 | PdBr$_2$(d*t*bpf) | 89 |
| 6 | PdI$_2$(d*t*bpf) | 12 |
| 7 | Pd$_2$(dba)$_3$/d*t*bpf | NR |

[a] Reaction conditions: 3 mmol of 4-chlorotoluene, 3.3 mmol of propiophenone, 0.06 mmol of catalyst , 3.3 mmol of NaO$^t$Bu, 3 mL of THF, 60°C, 3 h reaction time. [b] Conversion was determined by GC.

A comparison of the X-ray crystal structures of this series of catalysts revealed that the P-Pd-P bite angle of the bidentate ligand in PdCl$_2$(d*t*bpf) is the largest (104.22°) observed.[6a,8] Although the reported bite angle of the isopropyl analog, PdCl$_2$(dippf) is 103.95°,[8a] this catalyst did not exhibit comparable activity. This suggests that in addition to the larger bite angle, the bulky electron rich tertiary butyl groups on the phosphorus atom play a crucial role in providing the apt electronic and steric balance necessary to facilitate the oxidative addition and reductive elimination steps in the coupling of challenging aryl chloride substrates.

The substrate scope, using PdCl$_2$(d*t*bpf) as the catalyst, proved very broad, and included challenging arylbromides (Table 2) and aryl chlorides (Table 3).

**Table 2.** Room temperature PdCl$_2$(d*t*bpf)-catalyzed α-arylation of aryl bromides.



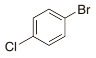
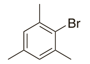
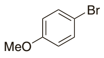
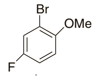
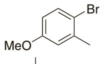
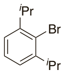
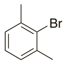
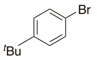
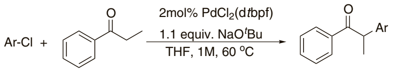
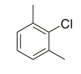
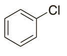
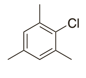
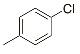
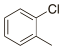
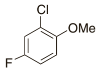
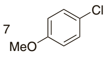
| entry | substrate | conv.(%)[b] | entry | substrate | conv.(%)[b] |
|---|---|---|---|---|---|
| 1 |  | 94 (92) | 5 |  | 86 (81) |
| 2 |  | 99 (97) | 6 |  | 86 (65) |
| 3 |  | 99 (97) | 7 |  | 13 |
| 4 |  | 99 (80) | 8 |  | 98 (96) |

**Table 3.** Effect of the aryl chloride substrate in the PdCl$_2$(d*t*bpf)-catalyzed α-arylation of propiophenone.



| entry | substrate | conv.(%)[a] | entry | substrate | conv.(%)[a] |
|---|---|---|---|---|---|
| 1 |  | 99 (86) | 4 |  | 99 (91) |
| 2 |  | 91 (90) | 5 |  | 96 (95) |
| 3 |  | 99 (93) | 6 |  | 93 (61) |
|  |  |  | 7 |  | 99 (94)[b] |

[a] Conversion was determined by GC. Isolated yields reported in parantheses. [b] The reaction was performed using dioxane at 100 °C.

In addition, a number of propiophenone and acetophenone derivatives could be successfully arylated using **Pd-118®**. Subsequent process development significantly reduced the catalyst loading.[7b]

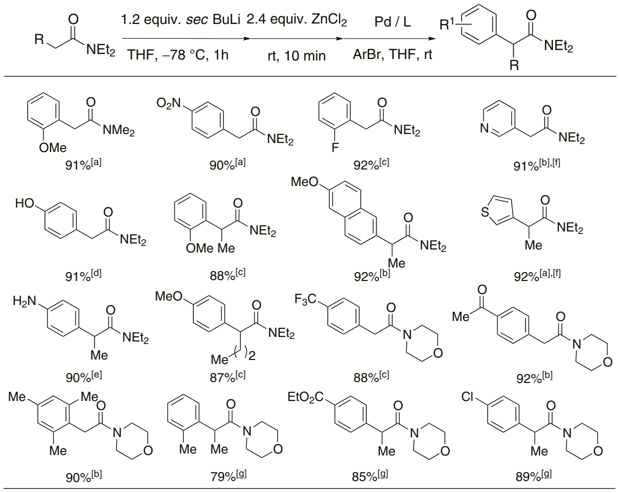
Johnson Matthey's portfolio has recently been extended with Pd(II) catalysts of the general formula (R-allyl)(PR$_3$)PdX that are showing promising activities in the α-arylation of propiophenone. Studies of these complexes are currently underway, in order to gain a more thorough knowledge of substrate scope and other processing specifics.

## Amides

The intermolecular α-arylation of Zn enolates of amides (Reformatsky conditions) has been reported in excellent yield under mild conditions with catalysts formed *in situ* from the hindered pentaphenyl-ferrocenyl di-*tert*-butylphosphine, **Q-Phos** with Pd(dba)$_2$, (**Pd-93**). The dimeric Pd(I) complex, [Pd(μ-Br)*t*-Bu$_3$P]$_2$, **Pd-113** has also been employed with great success under Reformatsky conditions. Depending on the substrate and conditions, the choice of the base becomes very critical. As an example, Hartwig has successfully employed *sec*-BuLi in the arylation of several substrates (Scheme 1).

---

7 (b) Grasa, G. A.; Colacot, T. J. *Org. Proc. Res. Dev.* **2008**, *12*, 522.
8 (a) PdCl$_2$(dippf): P-Pd-P = 103.59 – Elsagir, A. R.; Gassner, F.; Gorls, H.; Dinjus, E.; *J. Organomet. Chem.* **2000**, *597*, 139. (b) Hagopian, L. E.; Campbell, A. N.; Golen, J. A., Rheingold, A. L.; Nataro, C. J. *Organomet. Chem.* **2006**, *691*, 4890. (c) PdCl$_2$(dmpf): P-Pd-P = 99.3 – Bianchini, C.; Meli, A.; Oberhauser, W.; Parisel, S.; Passaglia, E.; Ciardelli, F.; Gusev, O. V.; Kal'sin, A. M.; Vologdin, N. V.; *Organometallics* **2005**, *24*, 1018. (d) PdCl$_2$(dppf): P-Pd-P = 97.98 – Butler, I. R.; Cullen, W. R.; Kim, T. J.; Rettig, S. J.; Trotter, J. *Organometallics* **1985**, *4*, 972.



**Scheme 1.** Hartwig's α-Arylation of Amides.

[a] 1 mol% Pd(dba)$_2$, 1 mol% Q-Phos [b] 2 mol% Pd(dba)$_2$, 2 mol% Q-Phos [c] 3 mol% Pd(dba)$_2$, 3 mol% Q-Phos [d] 0.5 mol% [Pd(μ-Br)*t*-Bu$_3$P]$_2$, 1.05 equiv. KH [e] 1 mol% [Pd(μ-Br)*t*-Bu$_3$P]$_2$, 1.05 equiv. KH [f] 70 °C [g] 4 mol% Pd(dba)$_2$, 4 mol% Q-Phos

## Esters

Recent work from Hartwig's lab, within the field of α-arylation of esters, established a general method suitable for a broad range of substrates, including aryl chlorides.[9] The work carried out demonstrated that **Pd-113** gives considerably better yield in comparison to the *in situ* system Pd(dba)$_2$/*t*-Bu$_3$P. For the bromides, the less expensive base Cy$_2$NLi can be used, while for aryl chlorides, NaHMDS is very effective (Table 4).

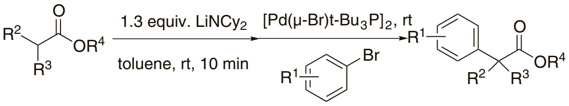
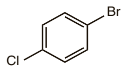
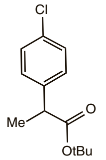
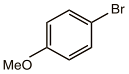
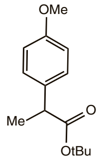
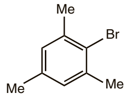
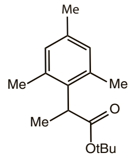
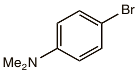
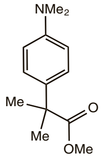
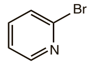
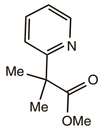
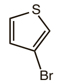
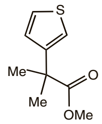
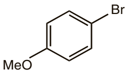
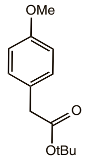
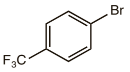
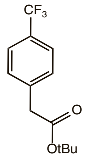


**Table 4.** α- Arylation Catalyzed by [P(μ-Br)t-Bu$_3$P]$_2$.

| entry | ArBr | catalyst loading [mol%] | product | yield [%] |
|---|---|---|---|---|
| 1 |  | 0.2 |  | 83 |
| 2 |  | 0.25 |  | 87 |
| 3 |  | 0.05 |  | 72 |
| 4 |  | 0.05 |  | 88 |
| 5 |  | 0.5 |  | 71 |
| 6 |  | 0.5 |  | 75 |
| 7 |  | 0.2 |  | 86 |
| 8 |  | 0.4 |  | 73 |

## Nitriles

The selective mono-arylation of acetonitrile and primary nitriles has been accomplished using α-silyl nitriles in the presence of ZnF$_2$ (Scheme 2).[10] For secondary nitriles, zinc cyanoalkyl reagents were used (Scheme 3). Palladium (0) complexes formed *in situ* from Pd$_2$(dba)$_3$, **Pd 94** or Pd(OAc)$_2$, **Pd 111** and *t*-Bu$_3$P or XantPhos were identified as efficient catalytic system for such transformations. An application of this methodology is the synthesis of verapamil, which could be realized in an overall 57% yield, starting from readily available isobutyronitrile.[10] Verapamil is a drug used in the treatment of heart disease for dialating the blood vessels in arteries.

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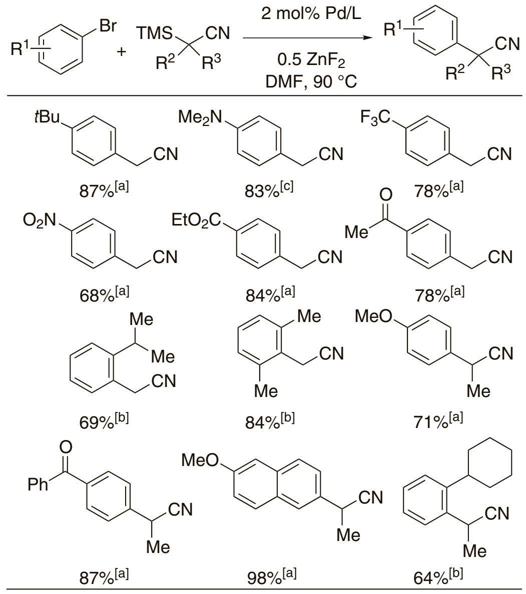
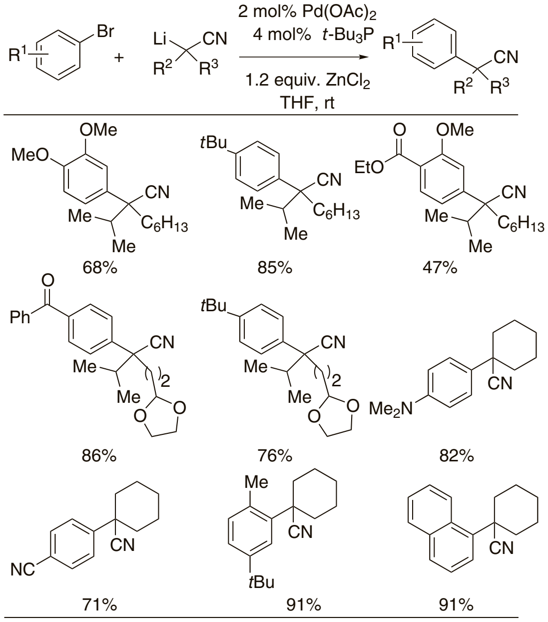
[9] (a) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176. (b) Hama, T.; Hartwig. J. F. *Org. Lett.* **2008**, *10*, 1545. (c) Hama, T.: Hartwig. J. F. *Org. Lett.* **2008**, *10*, 1549.

[10] Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824.



**Scheme 2.** Hartwig's mild α-arylation of TMS nitriles.

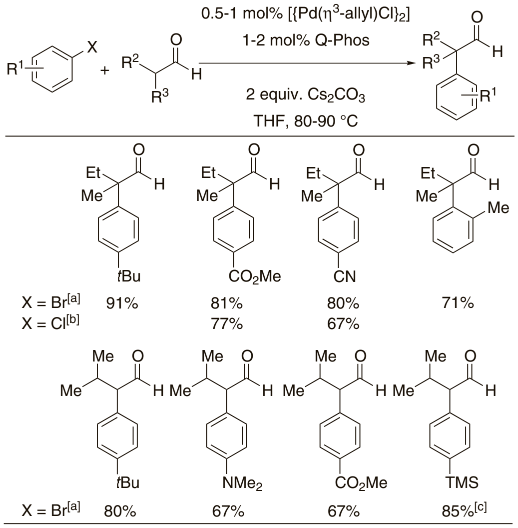
[a] 2 mol% $Pd_2(dba)_3$, 2 mol% XantPhos, 0.5 equiv. $ZnF_2$, DMF, 90 °C [b] 2 mol% $Pd_2(dba)_3$, 4 mol% $t$-$Bu_3P$, 0.5 equiv. $ZnF_2$, DMF, 90 °C [c] 2 mol% $Pd_2(dba)_3$, 4 mol% $PhPtBu_2$, 0.5 equiv. $ZnF_2$, DMF, 90 °C



**Scheme 3.** α-Arylation of Zinc Nitriles.

## Aldehydes

The α-arylation of aldehydes is very challenging due to the competing aldol condensations under the basic cross-coupling reaction conditions. Recent work from Hartwig's lab identified $[Pd(allyl)Cl]_2$, **Pd 110** in conjunction with **Q-Phos** and dppf as very efficient catalytic systems for both aryl bromide and -chloride substrates (Scheme 4).[11] Other methodologies employing bidentate aryl phosphines and alkyl phosphines are available, however, in many cases provide results inferior to Hartwig's process.[12] Johnson Matthey offers the fully formed Pd complexes of dppf, as well as the Q-Phos ligand.



**Scheme 4.** α-Arylation of Branched Aldehydes.

[a] 0.5 mol% APC, 1 mol% Q-Phos, 80°C [b] 1 mol% APC, 2 mol% Q-Phos, 90°C [c] 1 mol% APC, 4 mol% dppf in dioxane

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11 Vo, G. D.; Hartwig, J. F. *Angew. Chem.* **2008**, *120*, 2157; *Angew. Chem. Int. Ed.* **2008**, *47*, 2127.

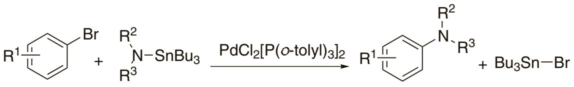
12 (a) Terao, Y.; Fukuoka, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 101. (b) Martin, R.; Buchwald, S. L. *Angew. Chem.* **2007**, *119*, 7374; *Angew. Chem. Int. Ed.* **2007**, *46*, 7236. (c) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505. (d) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177.

# 4.7.7 CARBON-HETEROATOM BOND FORMATION
## (Buchwald-Hartwig Coupling)

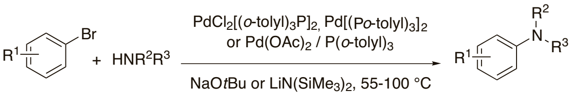
### C-N Bond Formation

The discovery that palladium complexes were able to catalyze the reaction between aryl halides and amines to form a new C-N bond revolutionized synthetic organic chemistry and initiated a flurry of activity in many research groups, both in academia and industry. As many compounds in the pharmaceutical, fine chemical and herbicidal industries contain arylamines, this finding introduced an extremely efficient alternative to the classical methods, such as reductive alkylation, copper-mediated chemistry carried out at high temperatures or nucleophilic substitution on electron-poor aromatic or heteroaromatic halides. As an alternative, aromatic nitration and catalytic reduction can be used (see Heterogeneous Catalysis Section 4.1).

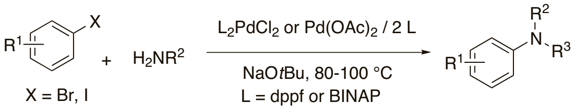
The pioneering studies carried out by Kosugi, Kameyama and Migita[1] reported the coupling of tin amides with aryl halides catalyzed by $PdCl_2[P(o\text{-tolyl})_3]_2$. The drawbacks of this methodology included low yields when using electron-rich or sterically hindered aryl bromides, as well as the toxicity associated with the tin reagent.



Inspired by this discovery, Hartwig, Buchwald and co-workers concurrently described the arylamine formation *via* a palladium catalyzed coupling reaction between aryl bromides and secondary amines.[2] This eliminated the need for the toxic and somewhat labile aminostannanes.

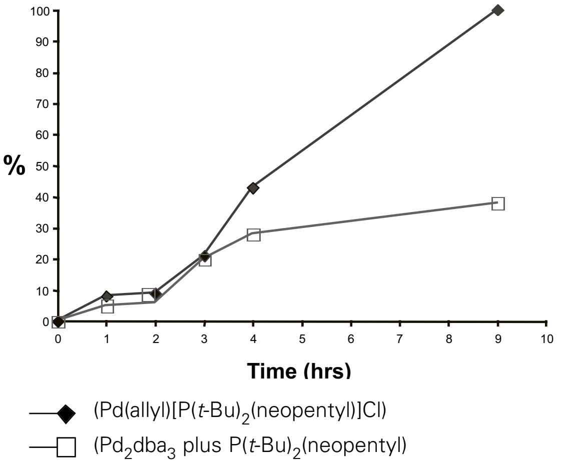


Subsequently, both research groups independently reported the extension of this methodology to encompass reactions of primary amines, employing catalysts containing aromatic bisphosphine ligands.[3] Hartwig *et al.* focused on the use of palladium complexes with dppf, whereas Buchwald and co-workers introduced palladium complexes of BINAP.



The attention of several research groups was subsequently focused on the development of catalytic systems containing bulky monodentate ligands.[4] A report by researchers at Tosoh company on the highly effective coupling reaction of aryl bromides and secondary amines in the presence of $Pd(OAc)_2$ in combination with *t*-Bu$_3$P,[5] led other groups such as Hartwig, Buchwald and Nolan to initiate studies on catalysts containing hindered electron rich ligands. Hartwig found that Pd(I) and Pd(0) catalysts of *t*-Bu$_3$P were able to catalyze the arylamine formation reaction with unactivated aryl bromides and aryl chlorides at relatively mild conditions, often at room temperature.[6] In particular, the palladium (I) dimer, $[Pd(\mu\text{-}Br)t\text{-}Bu_3P]_2$, resulted in remarkably efficient coupling reaction of aryl chlorides with secondary alkylamines.[7] The higher activity is presumably due to the formation of a "12 electron LPd(0) species".

A recent addition to this field involved the use of a catalyst formed by reacting P(*t*-Bu)$_2$(neopentyl) with $[Pd(allyl)Cl]_2$ to afford the palladium monomer, Pd(allyl)[P(*t*-Bu)$_2$(neopentyl)]Cl.[8] This precatalyst showed extremely high activity in the amination reactions of aryl bromides at room temperature and aryl chlorides at 80-100°C. The preformed catalyst (Pd(allyl)[P(*t*-Bu)$_2$(neopentyl)]Cl) is superior to the conventional *in situ* catalysts (Pd$_2$dba$_3$ plus P(*t*-Bu)$_2$(neopentyl) in terms of kinetics. This is also due to the generation of the highly active LPd(0) species.



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[1] Kosugi, M.; Kameyama, M; Migita, T. *Chem. Lett.* **1983**, 927.

[2] a) Guram, A. S.; Rennesl, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1995**, *34*, 1348 b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609 c) Paul F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.

[3] a) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215 b) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217 c) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144.

[4] a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131 b) Wolfe, J. P.; Wagaw, S.; Marcoux, J. –F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.

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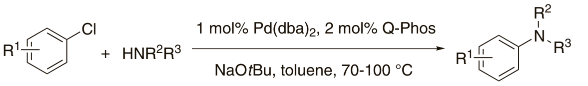
In addition to the application of the very effective monodentate alkyl phosphines, Hartwig and co-workers noted that palladium complexes containing the sterically hindered pentaphenylferrocene di-*tert*-butyl phosphine ligand, Q-Phos, mediated amination reactions in excellent yields.

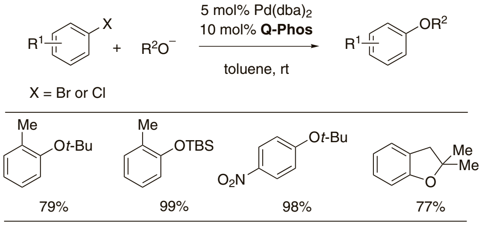


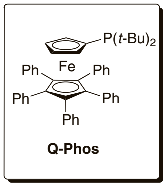
The substrate scope using the Q-Phos ligand encompassed both acyclic and cyclic secondary amines and primary amines, and both aryl chlorides or aryl bromides could be employed.[9] Based on Hartwig's study, Q-Phos is used with 0.1 mol% Pd loading, while $t$-Bu$_3$P is used at a higher Pd (0.5 mol %) loading for similar systems.

Depending on the nature of the aryl halide and the amine, a careful choice of conditions such as combination of catalyst (or catalyst precursor and ligand), base, solvent and temperature has been developed with a commercial perspective.

## C-O Bond Formation

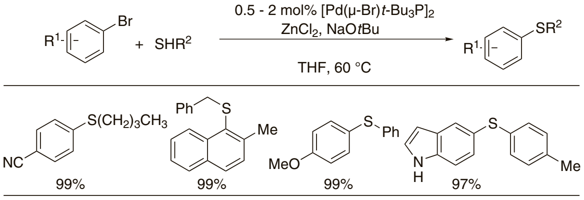
The most prominent reports on the palladium catalyzed Ar-O bond formations are the studies carried out by Hartwig and co-workers.[10] They observed aryl ether formation occurring at room temperature when the bulky ferrocenyl ligand Q-Phos was used in combination with a palladium precursor. Prior to this report, work carried out independently by Hartwig and Buchwald required temperatures greater than 100°C for successful ether formation.[11] Based on Hartwig's studies, a number of electron neutral and electron poor aryl halides could be coupled with *tert*-butoxide or siloxides using 5 mol% Pd(dba)$_2$/10 mol% Q-Phos at room temperature. The coupling of electron rich aryl halides was also possible, however, the reaction temperature had to be increased to 80°C.

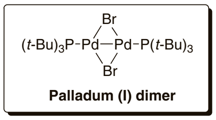




## C-S Bond Formation

The reports of metal catalyzed Ar-S bond formation reactions are very few, presumably due to the fact that many catalysts are poisoned by thiols. However, recently, Stambuli and co-workers reported a high-yielding thioetherification method using palladium (I) dimer [Pd(μ-Br)$t$-Bu$_3$P]$_2$.[12] The addition of ZnCl$_2$ to the reaction mixture proved crucial for any turnover of the reaction.





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[9] Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

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# 4.8 PARTICULATE CATALYSTS

Particulate catalysts are used in fixed-bed continuous gas phase or liquid phase reactions.

The dimensions of the catalyst bed (area of cross section and length), reactor design, and size and shape of the individual particulate (sphere, cylindrical tablet, ring, extrudate etc) are dictated by the requirements of heat transfer, fluid flow and pressure drop in the system.

For liquid phase reactions, the reactant, dissolved in a suitable solvent if necessary, is pumped into the column packed with catalyst. The reactant gas, usually hydrogen (or air-oxygen) can be passed co-currently or counter-currently through the catalyst bed. The product is collected continuously from the catalyst bed and no filtration of catalyst is involved. For gas phase reactions, only co-current flow is possible.

Since the formation of fine particles by attrition must be kept to a minimum, high mechanical strength is a fundamental requirement of all particulate catalysts.

The most commonly used particulate support in the fine chemicals industry is $\gamma$-alumina. Although not as strong as $\alpha$-alumina, the relatively high surface area (100–350 $m^2g^{-1}$) makes $\gamma$-alumina a more useful catalyst support than $\alpha$-alumina (typical surface area 1–10 $m^2g^{-1}$).

In some continuous gas phase reactions, the catalyst may become deactivated due to the deposition of coke on the active sites. In such cases the catalyst can be regenerated *in situ* by the controlled oxidation of the deposited material (to $CO_2$ and $H_2O$). However, great care must be taken to avoid excessive exotherm generation in the bed to prevent irreversible metal crystallite sintering with subsequent loss of catalyst activity.

Although not as strong as alumina, carbon can be used as a granular support in fixed bed reactors. It is used in cases where the aggressive/corrosive nature of the reactants makes the use of $\gamma$-alumina impossible, e.g.

$$Cl_2CHCOOH \longrightarrow ClCH_2COOH + HCl$$

The catalytic metal may be deposited on the outer surface of the shaped particulate support (eggshell deposition) or may be homogeneously impregnated throughout the bulk of the support (uniform deposition). For most purposes, the diffusion of reactants into the particulate bulk is slow, so eggshell catalytic metal loading is generally preferred.

Catalytic metal loadings on particulate supports are usually in the range 0.2-2% by weight with respect to the weight of support (as opposed to 1-10% for powdered catalysts).

Care should be exercised when charging particulate catalysts to fixed bed reactors to minimize physical damage and the generation of fines with increased pressure drop and metal loss consequences. Details of catalyst loading procedures are given in Section 2.1.3.

If catalyst to be used for a hydrogenation is supplied in an unreduced form, it needs to be activated in the reactor before use according to the following procedure:

(i) load the catalyst carefully into the reactor and flush away air with flowing nitrogen (or other inert gas) at ambient temperature. Ensure the volume of nitrogen exceeds 5 x the volume of the reactor.

(ii) introduce hydrogen at a concentration of 1% into the flowing nitrogen. Check for an exotherm in the catalyst bed. If it does not exceed 20°C, then slowly increase the temperature (over 60 minutes) up to the desired reaction temperature. The low hydrogen concentration will prevent a large exotherm when the catalyst species undergoes reduction.

(iii) check for any exotherm and gradually increase the hydrogen concentration to 100% hydrogen.

(iv) slowly introduce the feed to minimize any exotherms until the desired feed rate is achieved.

When the catalyst is finally discharged from the reactor, the above sequence should be reversed. It is very important to ensure that all traces of $H_2$ are removed and that the catalyst has fully cooled to ambient temperature before exposure to air.

## 4.8.1 Continuous Flow

Continuous flow processing offers many potential advantages over traditional batch manufacturing, and the pharmaceutical industry and other fine/specialty chemical sectors are investing in R&D efforts to explore the feasibility of this approach.

*See our range of Particulate Catalysts on page 65.*

In general, continuous processes have greater throughputs than their batch counterparts. Low residence times provide increased control of process variables such as heat transfer and mixing, thus reducing unwanted side reactions and final product degradation. Smaller reactors can be used to produce the same quantities of products, and waste production is often much lower.

For these reasons, continuous flow processing can provide a competitive advantage for the manufacturer.

In response to the growing interest in these production methods, Johnson Matthey offers a variety of Base and Precious Metal fixed bed catalysts designed specifically for continuous flow processing. The effectiveness of these particulate and shaped catalysts in continuous flow processes has been demonstrated in partnership with continuous flow equipment manufacturers.

Johnson Matthey fixed bed catalysts are available for both traditional heterogeneous and anchored homogeneous continuous flow application. Like their powdered catalyst counterparts, particulate PGM catalysts are used for a variety of reactions including hydrogenation, amination, dehydrogenation, hydrodehalogenation and isomerization.

### Applications for Johnson Matthey Particulate Catalysts in Organic Synthesis

| Catalyst Type | Support Material | Nominal Size/Shape | PGM | Loading (%wt) | Applications |
|---|---|---|---|---|---|
| 48 | Alumina | 3mm Tablets | Pd | 0.5 | Hydrogenation/Dehydrogenation |
| 49 | Alumina | 3mm Tablets | Pd | 2 | Hydrodehalogenation |
| 50 | Alumina | 3mm Tablets | Pd | 0.5 | Hydrogenation/Dehydrogenation |
| 50A | Alumina | 4–8mm Spheres | Pd | 0.5 | Hydrogenation/Dehydrogenation |
| 50B | Alumina | 2–4mm Spheres | Pd | 0.5 | Hydrogenation/Dehydrogenation |
| 54 | Alumina | 3mm Tablets | Pd | 0.5 | Hydrogenation of Phenol to Cyclohexanone, Amination of Ketones, Hydrogenation of Olefins, Aromatic Ring Hydrogenation |
| 86 | Carbon | 3mm Extrudate | Pd | 0.8 | Hydrogenation of Alkynes and Alkenes to Alkanes, Hydrodehalogenation |
| 300 | Alumina | 3mm Extrudate | Pd | 0.5 | Hydrogenation/Dehydrogenation |
| 301 | Alumina | 3mm Extrudate | Pd | 0.5 | Hydrogenation/Dehydrogenation |
| 309/6 | Alumina | 2.5mm Trilobe Extrudate | Pd |  | Selective Hydrogenation of Dienes |
| 352 | Alumina | 3x3mm Trilobe Extrudate | Pd |  | Hydrogenation of Phenol to Cyclohexanone |
| 353 | Alumina | 4-6 mm Spheres | Pd |  | Hydrogenation of Phenol to Cyclohexanone |
| 354 | Alumina | 4–6mm Spheres | Pd | 0.2 | Hydrogenation of Olefins |
| 355 | Alumina | 2–4mm Spheres | Pd | 0.5 | Hydrogenation of Olefins |
| 355 | Alumina | 5mm Spheres | Pd |  | Hydrogenation of Phenol to Cyclohexanone |
| 360 | Alumina | 3mm Tablets | Pd/Ru | 0.1/0.1 | Alkene to Alkane Hydrogenation |
| 375 | Carbon | 3mm Extrudate | Pd | 1 | Reductive Alkylation |
| 382 | Carbon | 2mm Extrudate | Pd | 2 | Hydrogenation/Dehydrogenation |
| 386 | Carbon | 2–5mm Granules | Pd | 1 | Hydrogenation of Olefins |
| 454 | Alumina | 4mm Ring Extrudate | Pd | 1 | Hydrogenation of Phenol to Cyclohexanone |
| 482 | Carbon | 2mm Extrudate | Pd | 2 | Hydrogenation |
| 73 | Alumina | 3mm Tablets | Pt | 0.3, 0.5 | Dehydrogenation, Aromatic Ring Hydrogenation, Benzene to Cyclohexane, Decomposition of Hydrogen Peroxide |
| 176 | Alumina | 4–8mm Spheres | Pt | 1 | Amination of Carbonyls, Dehydrogenation of Alcohols to Carbonyls |
| 146 | Alumina | 3mm Tablets | Ru | 0.5 | Hydrogenation of Aliphatic Carbonyls, Aromatic Ring Hydrogenation |
| 642 | Carbon | 2mm Extrudate | Ru | 3 | Hydrogenation of Aliphatic Carbonyls, Hydrogenation of Olefins, Aromatic Ring Hydrogenation |
| 660 | Silica | 1.5mm Extrudate | Ru | 3 | Hydrogenation of Carbonyls |
| 520 | Alumina | 3mm Tablets | Rh | 0.5 | Hydrogenation of Aromatics |
| PRICAT CU 60/35 | Silica | Powder | Cu |  | Hydrogenation (Aldehydes, Nitro Compounds) |
| PRICAT CU 60/35 | Silica | Trilobe Extrudate | Cu |  | Hydrogenation (Aldehydes, Nitro Compounds) |
| PRICAT CZ 30/18 | Zinc, Alumina | Trilobe Extrudate | Cu | *1) | Aldehyde Hydrogenation |
| PRICAT CZ 40/18 | Zinc, Alumina | Trilobe Extrudate | Cu | *1) | Aldehyde Hydrogenation |
| PRICAT NI 60/15 | Ni, Alumina, Kieselguhr | Powder | Ni |  | Hydrogenation |
| PRICAT NI 60/15 | Ni, Alumina, Kieselguhr | Trilobe Extrudate | Ni | *1) | Hydrogenation |
| PRICAT NI 62/15 | Ni, Alumina, Kieselguhr | Powder | Ni |  | Hydrogenation |

*1) These tablets are available in the following sizes (dxh in mm) 3.2x3.2mm, 5x4, 6x5, 10x6

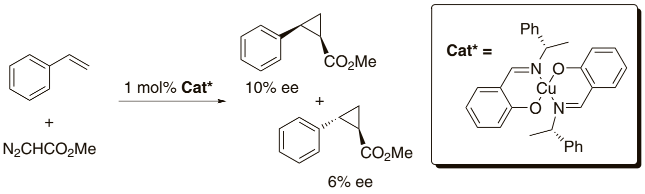
# 4.9 HOMOGENEOUS CHIRAL CATALYSIS

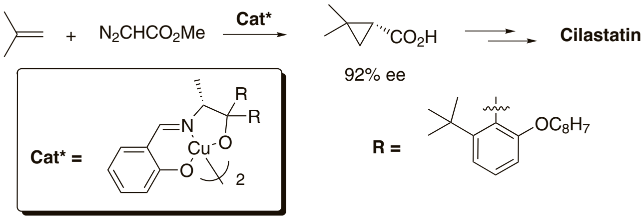
In 1992 the Food and Drug Administration in the U.S. introduced guidelines to encourage the commercialization of single-enantiomers drugs. This has driven the discovery of new and efficient methods to access enantiomerically pure compounds.

Traditionally, enantiomerically pure compounds have been obtained by classical resolution of racemates or transformation of naturally occurring chiral compounds, and more recently by chromatographic separation technologies. Biocatalysis is another important tool for the production of single enantiomers, but its applicability is limited by the inherent single-handed, lock-and-key specificity of enzymes. Since the late 1960s, asymmetric organometallic catalysis has become a very powerful strategy and is now recognized in industry as a cost-effective means of producing chiral intermediates and products.[1]

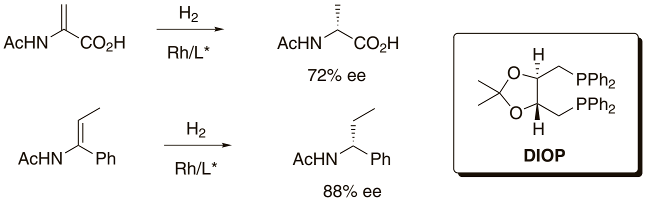
Asymmetric catalysis is achieved by the combination of a chiral ligand, a metal atom and, in some cases, an achiral additive or other auxiliary ligands. The chosen chiral ligand must have a suitable combination of structure and functionalities to modify the metal atom, generating reactivity and stereoselectivity.

The first examples of enantioselective organometallic catalysis can be traced back to 1966, when Noyori *et al.* described the cyclopropanation of alkenes using a salen-copper complex.[2] Although very low enantioselectivities (~10% ee) were initially reported, fine-tuning of the copper catalyst allowed Aratani to improve them to 92% ee.[3] This methodology was applied later on to the industrial preparation of cilastatin.





Knowles, Horner and Kagan[4] independently reported the first examples of homogeneous-catalyzed asymmetric hydrogenation of olefins employing Rh complexes bearing chiral phosphines. This novel methodology proved to be very successful and Monsanto used it in the preparation of the drug L-DOPA, in what became the first industrial asymmetric synthesis.[5]



These first achievements stimulated further investigations, and in 1980 Noyori published his first article on asymmetric hydrogenation of aminoacids employing chiral BINAP, based on the $C_2$ symmetric binaphthyl backbone.

The high chiral-recognition ability of BINAP-based metal complexes boosted the synthetic applications of asymmetric hydrogenation. Soon these complexes were also used in other catalytic reactions such as the asymmetric isomerization of allylic amines, a reaction employed by Takasago in the industrial synthesis of (-)-menthol from myrcene since 1985.[6]

Even more successful has been the use of BINAP-Ru complexes in the asymmetric hydrogenation of functionalized olefins and ketones. This reaction has been applied to the preparation of several drugs and natural products, including isoquinilone alkaloids.[7]

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[1] (a) Blaser H U (Ed.), Schmidt E (Ed.) Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions, Wiley VCH, **2003**, ISBN-10: 3527306315. (b) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J.J. *Chem.Rev.* **2006**, *106*, 2734. (c) Jaekel, C.; Paciello, R. *Chem.Rev.* **2006**, *106*, 2912. (d) Tang, W.; Zhang, X. *Chem.Rev.* **2003**, *103*, 3029.

[2] Nozaki, H.; Moruiti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, *22*, 5239-5244.

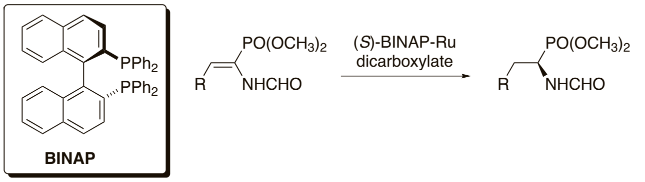
[3] Aratani, T, Pure and Appl. Chem **1985**, 57, 1839-1844.

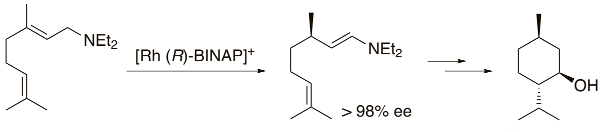
[4] Kagan, H. B.; Dang, T.-P. J. Am. Chem. Soc. **1972**, *94*, 6429–6433.

[5] Knowles W. S. Nobel Lecture Angew Chemie Intern Ed., **2002**, *41*, 1998-2007. (L-Dopa was commercially prepared with 95% ee using Dipamp Rh complexes).

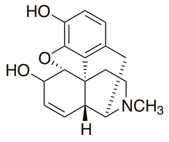
[6] Akutagava S, Tani K, in Catalytic Asymmetric Synthesis, Ed. Ojima, I., VCH, Weinheim, **2000**, 145-163, ISBN-10: 0471298050.

[7] Noyori, R., Nobel Lecture, *Angew. Chemie. Int. Ed.*, **2002**, 41, 2008-2022.

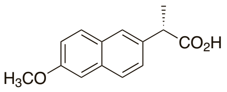




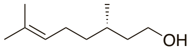
**(-)-Menthol**



**Morphine**



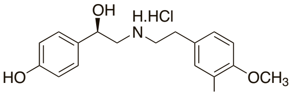
**Naproxen**



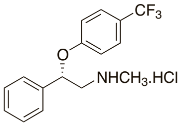
**Citronellol**

The asymmetric hydrogenation of simple, unfunctionalized ketones remained an unresolved problem until 1995. There Noyori *et al.* found a general solution based on the use of a [(phosphine) $RuX_2$ diamine)] complex in the presence of an alkaline base.[8] The newly devised bisphosphine/diamine complex proved to be very active and selective in the hydrogenation of a range of aromatic, heteroaromatic and olefinic ketones in 2-propanol containing *t*-BuOK or KOH.

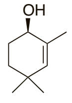
This method has been applied to the asymmetric synthesis of several drugs, including (*R*)-denopamine, the antidepresant (*R*)-fluoxetine and the antipsychotic (*S*)-duloxetine.[7]



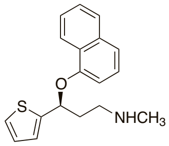
**denopamine hydrochloride**



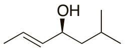
**fluoxetine hydrochloride**



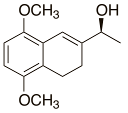
**precursor of α-damascone**



**duloxetine**



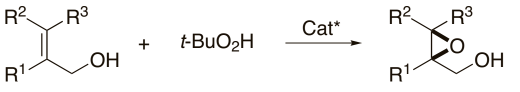
**precursor of α-tocopherol**



**precursor of anthracyclins**

Following the first discoveries in asymmetric hydrogenation, the search for new families of chiral phosphorous ligands with improved stereo-electronic characteristics has become an on-going effort both in academia and industry. Dr. Knowles and Prof. Noyori were awarded the Nobel Prize in Chemistry in 2001 for their outstanding contributions in this subject.

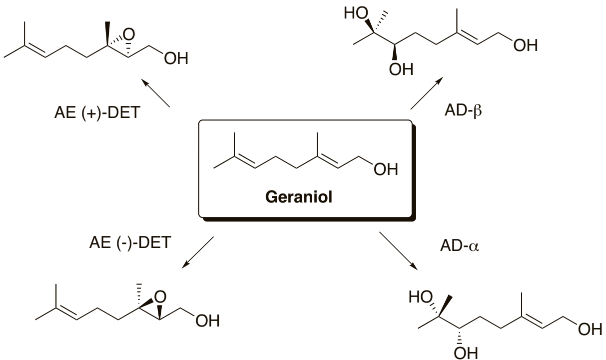
Prof. K. B. Sharpless also shared this 2001 Nobel Prize thanks to his innovative work in the asymmetric epoxidation of olefins.[9] In 1980 Katsuki and Sharpless discovered the titanium-catalyzed asymmetric epoxidation of olefins bearing allylic hydroxy groups.[10]



often > 95% ee

Cat* = diethyl tartrate + Ti(O*i*-Pr)$_4$

The osmium-catalyzed asymmetric dihydroxylation was subsequently discovered in 1987.[11] Mechanistic investigations and ligand engineering allowed the application of this second Sharpless reaction to any given class of alkenes, making it a very useful technology in organic synthesis.



AE - asymmetric epoxydation
AD - osmium-catalyzed asymmetric dihydroxylation

During the 1990s, Jacobsen and Katsuki independently developed chiral manganese-salen ligands for the catalytic epoxidation of alkenes in combination with cheap oxygen sources (i.e. NaClO), enantioselectivities often reaching 98% ee.

During the last decade many new enantioselective reactions have been discovered (aminohydroxylation, aziridination, hydroformylation). Catalysis by palladium complexes has been actively developed, particularly in the areas of enantioselective allylic substitution and asymmetric Heck reaction.[12]

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[8] (a) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed.* **1998**, *37*, 1703.(b) Noyori, R.; Koizumi, M.; Ishii, D.; Ohkuma, T. *Pure Appl. Chem*, **2001**, *73*, 227.

[9] Sharpless K B, Nobel Lecture, *Angew. Chemie. Int. Ed.*, **2002**, 41, 2024-2032.

[10] (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

[11] (a) Crispino, G. A.; Sharpless, K. B. Synthesis **1993**, *8*, 777. (b) Johnson, R. A.; Sharpless, K. B. in Catalytic Asymmetric Synthesis, Ed. Ojima, I., VCH, Weinheim, **2000**, 357-398, ISBN-10: 0471298050.

[12] Catalytic Asymmetric Synthesis, Ed. Ojima, I., VCH, Weinheim, **2010**, ISBN-13: 978-0470175774, to be published.

## 4.9.1 Asymmetric Hydrogenation

Homogeneous asymmetric hydrogenation is one of the core technologies that Johnson Matthey offers to its customers in the Pharmaceutical and Fine Chemical industries through its business unit, Catalysis and Chiral Technologies (CCT). The portfolio has been developed by combining in-licensed asymmetric ligands with in-house developed catalytic systems. A range of technologies has been assembled that allows the asymmetric hydrogenation of C=C, C=O and C=N bonds in a very broad range of substrates.[1]

We have listed our current range of commercially available catalysts in Table 7, Chiral Homogeneous Catalysts. If a catalyst which you require is not listed, please contact us, to confirm if the product is part of our development pipeline. We also offer development and scale up services as described in Section 3.

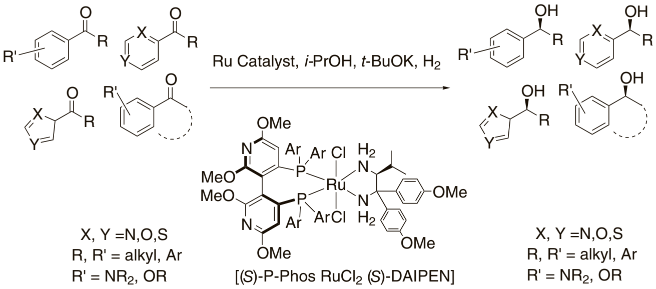
## 4.9.2 Asymmetric Ketone Reduction

### Ketone hydrogenation technology

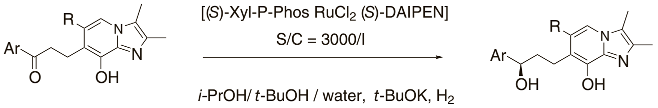
The discovery by Professor Noyori's group that non-functionalized aromatic ketones can be efficiently reduced by ruthenium catalysts of the type [(phosphine) $RuX_2$ (diamine)][2] was a dramatic leap forward in the field of asymmetric homogeneous hydrogenation.

The main scope of the reaction covers an array of substituted aromatic ketones, $\alpha$-$\beta$-unsaturated ketones and heteroaromatic ketones.[3] The reaction is usually carried out in *i*-PrOH in the presence of a catalytic amount of base, usually *t*-BuOK, 1-5 mol % with respect to the substrate, which is necessary to activate the ruthenium halide pre-catalyst. The reaction is compatible with the presence of various co-solvents (DMF, toluene, THF, etc.).

Noyori-type asymmetric reduction can usually be introduced at the development stage and replace a conventional, achiral hydride reduction without the need for changes in the overall synthetic route. The advantages over conventional hydride chemistry are remarkable and become more significant at larger scale. These advantages are the ease of use of the catalyst, very high activity at low catalyst loadings, no processing at low temperature and minimal requirement for reaction work up.



Many phosphine ligands can be utilized in ketone hydrogenation catalysis in complexes of the 'Noyori-type' [(phosphine) $RuCl_2$ (diamine)]. The P-Phos series of ligands are especially effective ligands for this catalysis when used in combination with 1,2-diamine ligands such as DPEN (1,2-diphenylethylenediamine) and DAIPEN (1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine). Upon optimization of the reaction conditions, the technology is widely applicable to complex molecules of industrial interest.[4]



The combination of chiral phosphines (P-Phos, Tol-P-Phos, Xyl-P-Phos, Binap, Tol-Binap) and diamines (DPEN, DAIPEN) gives rise to two pairs of diastereoisomers, of which the (S)/(S) and (R)/(R) isomers are usually used for the asymmetric hydrogenation of linear ketones while the (R)/(S) and (S)/(R) isomers may be preferred for the hydrogenation of cyclic ketones.

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[1] For recent reviews on asymmetric hydrogenation and industrial applications see: (a) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J.J. *Chem.Rev.* **2006**, *106*, 2734. (b) Jaekel, C.; Paciello, R. *Chem.Rev.* **2006**, *106*, 2912. (c) Tang, W.; Zhang, X. *Chem.Rev.* **2003**, *103*, 3029.

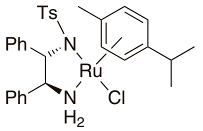
[2] Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed.* **1998**, *37*, 1703.

[3] For reviews see: (a) Nobel Lecture: Noyori, R. *Angew. Chem. Int. Ed.* **2002** *41*, 2008. (b) Noyori, T.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40 (c) Noyori, R., Kitamura, M.; Ohkuma, T. *PNAS*, **2004**, *101*, 5356 (d) Noyori, R.; Koizumi, M.; Ishii, D.; Ohkuma, T. *Pure Appl. Chem*, **2001**, *73*, 227.

[4] Palmer, A.; Zanotti-Gerosa, A.; Nedden, H. *Tetrahedron: Asymmetry* **2008**, *19*, 1310. Selected process patents: WO 2006136552, WO 2004011452.

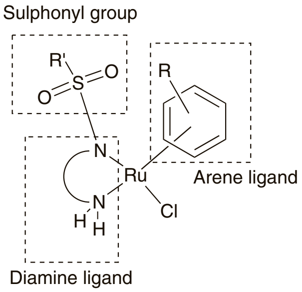
## Transfer hydrogenation technology

Ruthenium catalyzed transfer hydrogenation has a substrate scope similar to the Noyori hydrogenation.[5] The reduction of C=O groups can be carried out in the presence of *i*-PrOH and a suitable base (a reversible reaction with the possibility of kinetic resolution processes[6]) while the reduction of both C=O[7] and C=N groups[8] can be performed in the presence of a mixture of formic acid and triethylamine (an irreversible reaction). It has also been recently shown that transfer hydrogenation catalysts can reduce polarized C=C bonds.[9] The catalyst is modular and allows the easy modification of its three components: diamine ligand, sulfonyl substituent and arene ligand (arene = p-cymene, mesitylene, benzene, hexamethylbenzene).



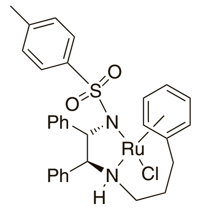
[(S,S)-Ts-DPEN-RuCl-(p-Cymene)]

Ts = p-toluenesulfonyl

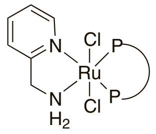


The use of different hydrogen sources or different reaction media can result in dramatic changes to the outcome of the reaction. Various groups have studied the effect of different solvents, reaction conditions and of different ratios of $Et_3N$ and HCOOH in an industrial context.[10] In addition, recent results indicate that the ruthenium transfer hydrogenation catalysts can be used without any modification in aqueous[11] or in biphasic organic solvent/water media.[12] Both HCOONa and $Et_3N$/HCOOH are suitable hydride donors under aqueous or biphasic conditions.

The Wills group has developed a tethered ruthenium transfer hydrogenation catalyst that displays enhanced stability and activity,[13] especially when poly-functionalised substrates are used. Baratta's group has significantly lowered catalyst loadings in the reduction with *i*-PrOH/base employing catalysts of the type [(phosphine) $RuCl_2$ Ampy] (Ampy = 2-aminomethylpyridine). For the hydrogenation of aliphatic ketones (in MeOH/base) the [(phosphine) $RuCl_2$ Ampy] complexes are also active hydrogenation catalysts.[14]



Tethered catalyst
[(S,S)-Ts-teth-DPEN-RuCl]

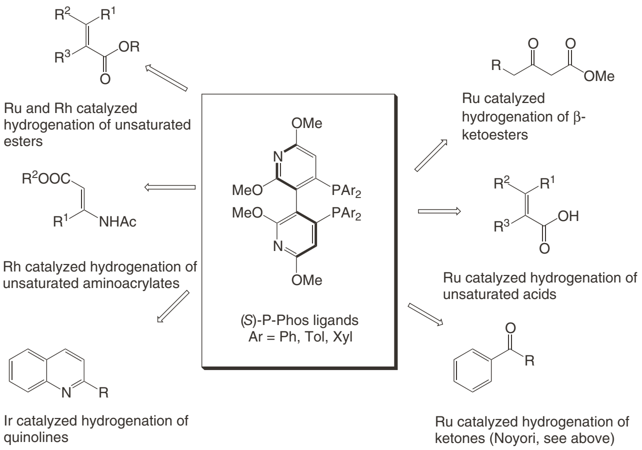


[(phosphine) $RuCl_2$ Ampy]

## 4.9.3 Chiral Phosphine Applications

The chiral phosphine ligands require metal precursors to synthesise a variety of catalysts. Ligand and metal precursor can be mixed prior to the addition of the substrate or in the presence of substrate forming *in-situ* the active catalyst. Alternatively, a variety of preformed rhodium and ruthenium complexes are available from Johnson Matthey.

### P-Phos and Xyl-P-Phos

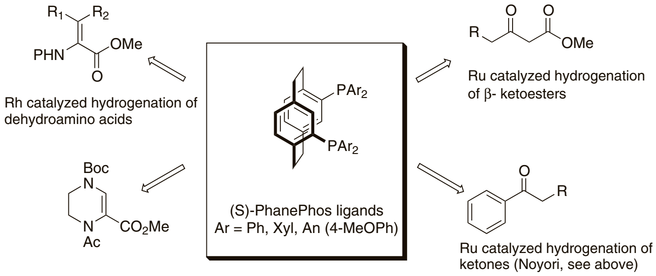


5 For reviews see: (a) Ikariya, T.; Murata, K.; Noyori,R. *Org. Biomol. Chem.* **2006**, *4*, 393. (b) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226.
6 Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed.* **1997**, *36*, 285.
7 Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521.
8 Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916.
9 Xue, D. ; Chen, Y.-C. ; Cui, X. ; Wang, Q.-W ; Zhu, J.; Deng, J.-G. *J. Org. Chem.* **2005**, *70*, 3584.
10 (a) Miyagi, M.; Takehara, J.; Collet, S.; Okano, K. *Org. Process. Res. Dev.* **2000**, *4*, 346. (b) Lennon, I. C.; Ramsden, J. A. *Org. Process Res. Dev.* **2005**, *9*, 110. (c) Selected process patent: WO 2007012793.
11 For a review see: Wu, X. ; Xiao, J. *Chem.Commun.* **2007**, 2449.
12 Ma, Y.; Liu, H.; Chen, L.; Cui, C.; Zhu, J.; Deng, J. *Org. Lett.* **2003**, *12*, 2103.
13 (a) Hayes, A. M.; Morris, D. J.; Clarkson, C. J.; Wills, M. *J. Am. Chem. Soc.* **2005**, *127*, 7318. (b) Cheung, F. K.; Hayes, A. M.; Hannedouche, J.; Yim, A. S. Y.; Wills, M. *J. Org. Chem.* **2005**, *70*, 3188.
14 Baratta, W.; Herdweck, E.; Siega, K.; Toniutti, M.; Rigo, P. *Organometallics,* **2005**, *24*, 1660. Sandoval, C.A.; Li, Y.; Ding, K.; Noyori, R. *Chemistry: Asian.J.* **2008**, *3*, 1801.
15 Selected process patents: WO 2008071951, WO 2008077560.
16 For a review see: Wu, J.; Chan, A. S. C. *Acc. Chem. Res.* **2006**, *39*, 711.

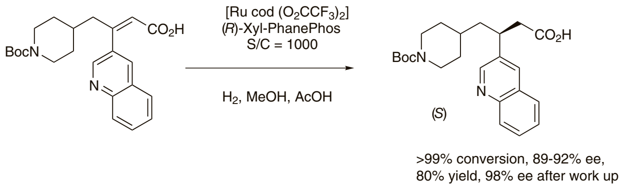
P-Phos, developed by Prof A. Chan, is an atropisomeric biaryl phosphine with the unique feature of incorporating two methoxy-substituted pyridine rings in the backbone. The P-Phos ligands often form more active and selective catalysts than the analogous BINAP ligands in a series of reactions[15] such as ruthenium catalyzed hydrogenation of β-ketoesters, rhodium and ruthenium catalyzed hydrogenation of dehydroamino acids and ruthenium catalyzed hydrogenation of non-functionalized ketones and unsaturated acids. Iridium-P-Phos catalysts have been recently used for the asymmetric hydrogenation of C=N bonds in quinolines.[16]

## PhanePhos and TCFP

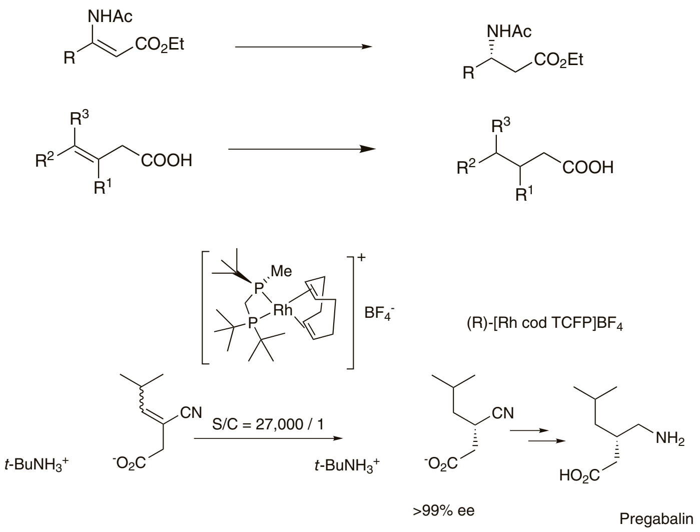
PhanePhos was first reported in 1997, and has since found applications in rhodium-catalyzed hydrogenation of dehydroaminoacids, ruthenium-catalyzed hydrogenation of ß-ketoesters, and ruthenium-catalyzed hydrogenation of non-functionalized ketones.[17] Both rhodium[18] and ruthenium catalysts bearing the PhanePhos ligand show an exceptionally high activity in most homogeneous hydrogenation reactions.



Xyl-PhanePhos in combination with [Ru cod $(O_2CCF_3)_2$] has been applied in the efficient asymmetric hydrogenation of an α-β-unsaturated acid, which is an intermediate in the synthesis of an $\alpha_v\beta_3$-integrin antagonist intermediate.[19]



TCFP is a bulky electron-rich P-chiral phosphine. Coordinated to rhodium, TCFP yields an extremely active catalyst for the effective hydrogenation of β-*N*-acetyl-aminoacrylates and β,γ-unsaturated acids.[20]



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17 (a) Rossen, K.; Pye, P. J.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207. (b) Pye, P. J.; Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 4441. (c) Burk, M. J.; Hems, W. P.; Herzberg, D.; Malan, C.; Zanotti-Gerosa, A. *Org. Lett.* **2000**, *2*, 4173. (d) Paracyclophane-based catalysts for ketone hydrogenation from JM CCT: Dominguez, B.; Zanotti-Gerosa, A.; Hems, W. *Org. Lett.* **2004**, *6*, 1927.

18 Selected process patent: US 2008171892.

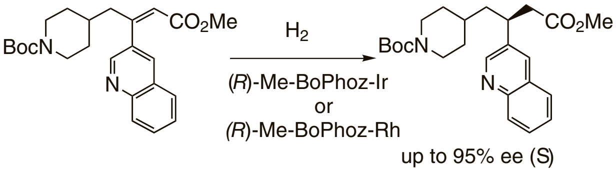
19 Grasa G. A.; Zanotti-Gerosa A.; Ghosh, S.; Teleha, C. A.; Kinney, W. A.; Maryanoff, B. E. *Tetrahedron Lett.* **2008**, *49*, 5328.

20 (a) Wu, H.-P.; Hoge, G.; *Org. Lett.* **2004**, *6*, 3645. (b) Gridnev, I. D.; Imamoto, T.; Hoge, G.; Kouchi, M.; Takahashi, M. *J. Am. Chem. Soc.* **2008**, *130*, 2560.

## Amino-phosphine Ligands

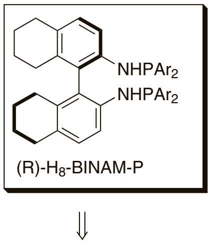
BoPhoz® is a phosphine-aminophosphine ligand based on the ferrocene backbone. This class of ligands has proven to be exceptionally active in many rhodium-catalyzed hydrogenations (S/C up to 100,000 in C=C hydrogenation)[21] as well as being used in ruthenium-catalyzed reactions.[22] The class of BoPhoz® ligands also offers the structural and electronic variety that may be required for the full optimization of the desired transformation.

More recently, Me-BoPhoz® has been employed in combination with Rh or Ir precursors in the asymmetric hydrogenation of an unsaturated ester in the enantioselective synthesis of an $\alpha_v\beta_3$ integrin antagonist intermediate.[23]

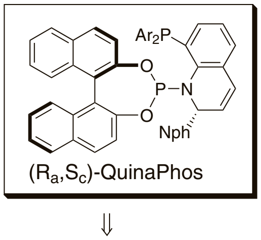


$H_8$-BINAM-P is an amino-phosphine ligand with axial chirality characterized by a larger than usual dihedral angle that is a consequence of the partially reduced binaphthyl backbone.[24]

QuinaPhos is a novel bidentate phosphine-phosphoramidate ligand that has been developed by the group of Prof. Leitner.[25] The versatility of the phosphine-phosphoramidate motif makes it applicable in a number of catalytic transformations, including rhodium-catalyzed asymmetric hydroformylation, rhodium-catalyzed asymmetric hydrogenation of functionaliszed alkenes and ruthenium-catalyzed asymmetric hydrogenation of ketones.[26]



Rh-catalyzed hydrogenations of
dehydroaminoacids and enamides



Rh-catalyzed hydrogenations of
dehydroamino acids and hydroformylation,
and Ru-catalyzed hydrogenation of ketones

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[21] (a) Boaz, N. W.; Debenham, S. D.; Mackenzie, E. B.; Large, S. E. *Org. Lett.*, **2002**, *4*, 2421. (b) Boaz, N. W.; Mackenzie, E. B.; Debenham, S. D.; Large, S. E.; Ponasik, Jr., J. A. *J. Org. Chem.* **2005**, *70*, 1872.

[22] (a) Boaz, N. W.; Large, S.E.; Ponasik, Jr., Tetrahedron Lett. **2006**, *47*, 4033. (b) WO 2006/016116 A1 to Phoenix Chemicals based on work done in collaboration with JM CCT.

[23] Zanotti-Gerosa, A.; Kinney, W. A.; Grasa, G. A.; Medlock, J.; Seger, A.; Ghosh, S.; Teleha, C. A.; Maryanoff B.A. *Tetrahedron: Asymmetry* **2008**, *19*, 938.

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[25] Franciò, G.; Faraone, F.; Leitner, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 1428.

[26] Burk, S.; Franciò, G.; Leitner, W. *Chem. Commun.* **2005**, 3460.

## 5. Table: Heterogeneous Catalysts (US Manufactured)

| Catalyst Type | Support Material | Metal Loading % | Typical Applications |
|---|---|---|---|
| **PALLADIUM** | | | |
| A101023-10 | Carbon Powder | 10 | Dehydrogenation |
| A101038-10 | Carbon Powder | 10 | Dehydrogenation |
| A102023-5 | Carbon Powder | 5 | Hydrogenation of alkynes, alkenes, aromatic rings, nitro and nitroso compounds, imines, nitriles, aromatic carbonyls, reductive alkylation, reductive amination, hydrogenolysis, debenzylation, selective oxidation, dehydrogenation, C-C coupling |
| A102038-5 | Carbon Powder | 5 | Hydrogenation of alkynes, alkenes, aromatic rings, aromatic carbonyls, hydrogenolysis, debenzylation, selective oxidation, dehydrogenation |
| A103038-5 | Carbon Powder | 5 | Selective hydrogenation where lower activity is required |
| A105023-5 | Carbon Powder | 5 | Conversion of phenol to cyclohexanone |
| A109047-5 | Carbon Powder | 5 | Hydrogenation of aromatic nitriles, imines, oximes, reductive amination, reductive alkylation, C-C coupling |
| A201053-10 | Barium Sulfate | 10 | Selective hydrogenation where lower activity is required |
| A201053-5 | Barium Sulfate | 5 | Selective hydrogenation where lower activity is required |
| A302011-5 | Alumina Powder | 5 | Selective hydrogenation where lower activity is required |
| A302023-5 | Carbon Powder | 5 | Rosenmund Reduction |
| A302038-5 | Carbon Powder | 5 | Rosenmund Reduction |
| A302085-5 | Carbon Powder | 5 | Rosenmund Reduction |
| A302099-5 | Alumina Powder | 5 | Selective hydrogenation where lower activity is required |
| A303060-5 | Calcium Carbonate | 5 | Selective hydrogenation where lower activity is required |
| A305060-5 | Calcium Carbonate | 5 | Selective hydrogenation of alkynes to alkenes |
| A306060-5 | Calcium Carbonate | 5 | Selective hydrogenation of alkynes to alkenes |
| A308053-5 | Barium Sulfate | 5 | Selective hydrogenation where lower activity is required |
| A401002-20 | Carbon Powder | 20 | Hydrogenolysis, debenzylation |
| A401102-5 | Carbon Powder | 5 | Hydrogenation of aromatic and aliphatic nitro compounds |
| A402002-5 | Carbon Powder | 5 | Hydrogenation of alkynes, alkenes, hydrogenolysis, hydrodehalogenation, debenzylation |
| A402028-10 | Carbon Powder | 10 | Hydrogenolysis, debenzylation |
| A402028-5 | Carbon Powder | 5 | Hydrogenolysis, debenzylation |
| A402032-10 | Carbon Powder | 10 | Hydrogenolysis, debenzylation |
| A405028-5 | Carbon Powder | 5 | Hydrogenation of alkynes, alkenes, aromatic and aliphatic nitro compounds, hydrogenolysis, hydrodehalogenation, debenzylation, C-C coupling |
| A405032-5 | Carbon Powder | 5 | Hydrogenolysis, debenzylation |
| A405038-5 | Carbon Powder | 5 | Hydrogenation of alkynes, alkenes, hydrogenolysis, hydrodehalogenation, debenzylation, C-C coupling |
| A501023-10 | Carbon Powder | 10 | Hydrogenolysis, debenzylation, dehydrogenation |
| A501032-10 | Carbon Powder | 10 | Hydrogenolysis, debenzylation |
| A501038-10 | Carbon Powder | 10 | Dehydrogenation |

| Catalyst Type | Support Material | Metal Loading % | Typical Applications |
|---|---|---|---|
| **PALLADIUM – CONTINUED** | | | |
| A503023-5 | Carbon Powder | 5 | Hydrogenation of alkynes, alkenes, aromatic rings, nitro and nitroso compounds, imines, nitriles, aromatic carbonyls, reductive alkylation, reductive amination, hydrogenolysis, debenzylation, selective oxidation, dehydrogenation, C-C coupling, isomerization |
| A503032-5 | Carbon Powder | 5 | Hydrogenation of nitro and nitroso compounds, imines, nitriles, oximes, reductive alkylation, reductive amination, hydrogenolysis, debenzylation |
| A503038-5 | Carbon Powder | 5 | Hydrogenation of aromatic carbonyls, hydrogenolysis, hydrodehalogenation, isomerization |
| A503129-5 | Carbon Powder | 5 | Hydrogenation of nitro and nitroso compounds, imines, nitriles, oximes, reductive alkylation, reductive amination, hydrogenolysis, debenzylation |
| A505085-5 | Carbon Powder | 5 | Hydrogenation of aromatic and aliphatic nitroso |
| A701023-5 | Carbon Powder | 5 | Rosenmund Reduction |
| **PLATINUM** | | | |
| B101002-5 | Carbon Powder | 5 | Selective oxidation |
| B101032-3 | Carbon Powder | 3 | Hydrogenation of halonitroaromatics |
| B101038-1 | Carbon Powder | 1 | Hydrogenation of halonitroaromatics |
| B102022-5 | Carbon Powder | 5 | Hydrogenation of heterocyclic compounds |
| B102032-1 | Carbon Powder | 1 | Hydrogenation of halonitroaromatics, p-aminophenol production |
| B102032-3 | Carbon Powder | 3 | Reductive alkylation |
| B103018-5 | Carbon Powder | 5 | Hydrogenation of alkenes, aromatic rings, heterocyclic compounds, aromatic and aliphatic nitro and nitroso compounds, imines, nitriles, aliphatic carbonyls, dehydrogenation, selective oxidation |
| B103032-3 | Carbon Powder | 3 | Hydrogenation of halonitroaromatics |
| B103032-5 | Carbon Powder | 5 | Hydrogenation of alkenes, aromatic rings, heterocyclic compounds, aromatic and aliphatic nitro and nitroso compounds, imines, nitriles, aliphatic carbonyls, dehydrogenation, selective oxidation |
| B104032-3 | Carbon Powder | 3 | Reductive alkylation |
| B104032-5 | Carbon Powder | 5 | Reductive alkylation |
| B105032-3 | Carbon Powder | 3 | Reductive alkylation |
| B105047-1 | Carbon Powder | 1 | Hydrogenation of halonitroaromatics, p-aminophenol production |
| B106032-3 | Carbon Powder | 3 | Reductive alkylation |
| B106032-5 | Carbon Powder | 5 | Reductive alkylation |
| B109032-5 | Carbon Powder | 5 | Reductive alkylation |

| Catalyst Type | Support Material | Metal Loading % | Typical Applications |
|---|---|---|---|
| **PLATINUM – CONTINUED** | | | |
| B111022-5 | Carbon Powder | 5 | Selective oxidation |
| B112002-5 | Carbon Powder | 5 | Selective oxidation |
| B301013-5 | Alumina Powder | 5 | Hydrosilylation |
| B301099-5 | Alumina Powder | 5 | Hydrosilylation |
| B501018-5 | Carbon Powder | 5 | Hydrogenation of alkenes, aromatic rings, heterocyclic compounds, aromatic and aliphatic nitro and nitroso compounds, imines, nitriles, aliphatic carbonyls, dehydrogenation, selective oxidation |
| B501032-5 | Carbon Powder | 5 | Hydrogenation of alkenes, aromatic rings, heterocyclic compounds, aromatic and aliphatic nitro and nitroso compounds, imines, nitriles, aliphatic carbonyls, dehydrogenation, selective oxidation |
| B503032-5 | Carbon Powder | 5 | Selective oxidation |
| **RHODIUM** | | | |
| C101023-5 | Carbon Powder | 5 | Hydrogenation of aromatic rings, heterocyclic compounds, aliphatic nitro compounds, aliphatic nitriles, alkenes |
| C101038-5 | Carbon Powder | 5 | Hydrogenation of aromatic rings, heterocyclic compounds, aliphatic nitro compounds, aliphatic nitriles, alkenes |
| C301011-5 | Alumina Powder | 5 | Hydrogenation of aromatic rings |
| **RUTHENIUM** | | | |
| D101023-5 | Carbon Powder | 5 | Hydrogenation of aromatic rings, heterocyclic compounds, aliphatic carbonyls, sugar hydrogenation, selective oxidation |
| D101002-5 | Carbon Powder | 5 | Hydrogenation of aromatic rings, heterocyclic compounds, aliphatic carbonyls, sugar hydrogenation, selective oxidation |
| D101038-5 | Carbon Powder | 5 | Hydrogenation of aromatic rings, heterocyclic compounds, aliphatic carbonyls, sugar hydrogenation, selective oxidation |
| D103002-5 | Carbon Powder | 5 | Selective oxidation |
| D302011-5 | Carbon Powder | 5 | Hydrogenation of aromatic rings, heterocyclic compounds, aliphatic carbonyls |
| **MIXED METALS** | | | |
| E101049-4/1 | Carbon Powder | 4% Pd 1% Pt | Hydrogenation of alkenes, nitro and nitroso compounds, imines, selective oxidation |
| E101023-4/1 | Carbon Powder | 4% Pd 1% Pt | Hydrogenation of alkenes, nitro and nitroso compounds, imines, selective oxidation |
| F101023-4.5/0.5 | Carbon Powder | 4.5% Pd 0.5% Rh | Hydrogenation of aromatic rings, heterocyclic compounds, aliphatic nitriles, oximes |
| F101038-4.5/0.5 | Carbon Powder | 4.5% Pd 0.5% Rh | Hydrogenation of aromatic rings, heterocyclic compounds, aliphatic nitriles, oximes |
| G101038-5/0.25 | Carbon Powder | 5% Ru 0.25% Pd | Hydrogenation of aromatic rings, heterocyclic compounds, aliphatic carbonyls |

**NOTE**

Paste catalysts are free flowing, powder–like materials, containing approximately 50–60% w/w water.
The foregoing lists of catalysts and usually applications are not exhaustive

# 5. Table: Heterogeneous Catalysts (UK Manufactured)

| Catalyst Type | Support Material | Metal Loading % | Typical Applications |
|---|---|---|---|
| **PALLADIUM** | | | |
| 21 | Calcium Carbonate | 5 | Selective hydrogenation e.g. alkyne to alkene in presence of a catalyst modifier (Lindlar) |
| 29A | Barium Sulphate | 5 | Selective hydrogenation where low activity is required |
| 31 | Silica-alumina powder | 2 | Hydrogen peroxide production by AQ process |
| 36 | Carbon powder/paste | 5 | Hydrodehalogenation |
| 37 | Carbon powder/paste | 3, 5 | Aromatic nitro group hydrogenation under mild conditions |
| 38H | Carbon powder/paste | 3, 5 | Hydrogenation of aromatic and aliphatic nitro/nitroso groups, Carbonyl hydrogenation, Hydrogenolysis e.g. Dehalogenation, N–Debenzylation |
| 39 | Carbon powder/paste | 5, 10 | Debenzylation, C–N and C–O cleavage, Alkene hydrogenation |
| 58 | Carbon powder/paste | 3, 5, 10 | Hydrogenation of aromatic and aliphatic nitro groups, Reductive alkylation/amination, Hydrogenation of aromatic nitriles to 1°-amines |
| 87G | Carbon powder | 3, 5 | Dehydrogenation |
| 87L | Carbon powder/paste | 3, 5, 10 | Hydrogenation of alkynes and alkenes to alkanes, Aromatic nitro hydrogenation, Aromatic aldehyde and ketone hydrogenation to alcohols, Hydrogenolysis e.g.Dehalogenation, C–N and C–O cleavage, Rosenmund reduction, Rosin disproportionation, Reductive alkylation/amination, Selective oxidation |
| 90 | Carbon powder/paste | 5, 10 | Aromatic nitro group hydrogenation, Hydrogenation of alkenes to alkanes. Debenzylation |
| 91 | Carbon powder/paste | 20, 10 | Debenzylation (Pearlman's catalyst) |
| 315 | Carbon powder/paste | 5, 10 | Alkene hydrogenation |
| 325 | Alumina powder | 5 | Selective hydrogenation where low activity required |
| 335 | Alumina powder | 2 | Hydrogen peroxide production by AQ Process. Selective oxidation |
| 338M | Carbon powder/paste | 5 | Hydrogenation of aromatic and aliphatic nitro/nitroso groups, Carbonyl hydrogenation, Hydrogenolysis e.g. Dehalogenation, N–Debenzylation |
| 369 | Carbon powder/paste | 5 | Hydrogenation of phenols to cyclohexanones |
| 373 | Carbon powder/paste | 10 | Selective hydrogenation of nitrate to hydroxylamine |
| 374 | Carbon powder/paste | 5, 10 | Aromatic carbonyls to alcohols, Aromatic nitro compounds, Alkenes |
| 392 | Carbon powder/paste | 5 | Debenzylation, dehalogenation |
| 393 | Carbon powder/paste | 5, 10 | Debenzylation, C–N and C–O cleavage, Alkene hydrogenation |
| 394 | Carbon powder/paste | 3, 5 | Debenzylation, C–N and C–O cleavage, Alkene hydrogenation |
| 395 | Carbon powder/paste | 3, 5 | Debenzylation, C–N and C–O cleavage, Alkene hydrogenation |
| 398 | Carbon powder/paste | 3, 5 | Alkene hydrogenation, Nitro group hydrogenation, C–N cleavage |
| 405 | Calcium carbonate | 5 | Selective hydrogenation |

| Catalyst Type | Support Material | Metal Loading % | Typical Applications |
|---|---|---|---|
| **PALLADIUM – CONTINUED** | | | |
| 434 | Carbon powder/paste | 5, 10 | Nitro compounds, Alkenes, Carbonyl compounds, Reductive alkylation, Nitrile hydrogenation |
| 436 | Carbon powder/paste | 3, 5 | Aromatic nitro group hydrogenation under mild conditions |
| 437 | Carbon powder/paste | 3, 5 | Aromatic nitro group hydrogenation under mild conditions |
| 438 | Carbon powder/paste | 3, 5 | Hydrogenation of aromatic and aliphatic nitro/nitroso groups, Carbonyl hydrogenation, Hydrogenolysis e.g. Dehalogenation, N–Debenzylation |
| 440 | Carbon powder/paste | 5 | Debenzylation, C–N and C–O cleavage, Alkene hydrogenation |
| 450 | Graphite powder | 5 | Imine hydrogenation, Selective hydrogenation |
| 458 | Carbon powder/paste | 3, 5 | Hydrogenation of aromatic and aliphatic nitro groups, Reductive alkylation/amination, Hydrogenation of aromatic nitriles to 1°-amines |
| 477 | Carbon powder/paste | 3, 5, 10 | Hydrogenation of alkynes and alkenes to alkanes, Aromatic nitro hydrogenation, Aromatic aldehyde and ketone hydrogenation to alcohols, Hydrogenolysis e.g.Dehalogenation, C–N and C–O cleavage, Rosenmund reduction, Rosin disproportionation, Reductive alkylation/amination, Selective oxidation |
| 487 | Carbon powder/paste | 3, 5, 10 | Hydrogenation of alkynes and alkenes to alkanes, Aromatic nitro hydrogenation, Aromatic aldehyde and ketone hydrogenation to alcohols, Hydrogenolysis e.g.Dehalogenation, C–N and C–O cleavage, Rosenmund reduction, Rosin disproportionation, Reductive alkylation/amination, Selective oxidation |
| 490 | Carbon powder/paste | 5, 10 | Aromatic nitro group hydrogenation, Hydrogenation of alkenes to alkanes. Debenzylation |
| **PLATINUM** | | | |
| 18 | Carbon powder/paste | 1, 5, 10 | Schiff's base and nitro hydrogenation, Aromatic ring hydrogenation, Hydrogenation of alkenes, Hydrogenation of aliphatic carbonyls to alcohols, Selective oxidation |
| 18MA | Carbon powder/paste | 1, 5 | Pyridine ring hydrogenation, Hydrogenation of halonitroaromatics and aliphatic nitro groups |
| 94 | Alumina powder | 5 | Selective hydrogenation, Hydrogenation of aliphatic ketones to alcohols in bulky molecules, chiral hydrogenation |
| 95 | Carbon powder/paste | 1 | Schiff's base and nitro hydrogenation |
| 103 | Carbon powder/paste | 1, 5 | Halonitroaromatics, Reductive alkylation, Alkenes |
| 117 | Carbon powder/paste | 1, 5 | Pyridine ring hydrogenation, Hydrogenation of halonitroaromatics and aliphatic nitro groups |
| 124 | Alumina powder | 5 | Selective hydrogenation where low activity is required |
| 128M | Carbon powder/paste | 1, 3, 5 | Schiff's base and nitro hydrogenation, Aromatic ring hydrogenation, Hydrogenation of alkenes, Hydrogenation of aliphatic carbonyls to alcohols, Selective oxidation |
| 130 | Carbon powder/paste | 5 | Schiff's base and nitro hydrogenation, hydrosilylation |
| 156 | Carbon powder/paste | 1, 2, 3 | Hydrogenation of halonitroaromatics and aromatic nitro groups, p–aminophenol production from nitrobenzene |
| 199 | Carbon powder/paste | 1,5 | Halonitroaromatics, Reductive alkylation, Alkenes |
| 200 | Carbon powder/paste | 1 | Hydrogenation of halonitroaromatics and aromatic nitro groups, Reductive alkylation |
| 287 | Graphite powder | 5 | Hydrogenation of aliphatic carbonyls, Selective oxidation |
| 289 | Graphite powder | 5 | Cinnamaldehyde to Cinnamyl Alcohol. Selective oxidation |

| Catalyst Type | Support Material | Metal Loading % | Typical Applications |
|---|---|---|---|
| **RHODIUM** | | | |
| 20A | Carbon powder/paste | 5 | Aromatic ring hydrogenation, Hydrogenation of alkenes to alkanes |
| 524 | Alumina powder | 5 | Aromatic ring hydrogenation, Hydrogenation of alkenes to alkanes |
| 526 | Alumina powder | 5 | Aromatic ring hydrogenation, Hydrogenation of alkenes to alkanes, but especially for bulky molecules |
| 551 | Graphite powder | 5 | Aromatic ring hydrogenation |
| 592 | Carbon powder/paste | 5 | Aromatic ring hydrogenation, Hydrogenation of alkenes to alkanes |
| 594 | Carbon powder/paste | 5 | Aromatic ring hydrogenation, Hydrogenation of alkenes to alkanes |
| **IRIDIUM** | | | |
| 30 | Calcium Carbonate | 5 | Selective hydrogenation of alkenes to alkanes, Aliphatic carbonyls to alcohols |
| 728 | Graphite powder | 5 | α-β unsaturated aldehydes to unsaturated alcohols |
| **RUTHENIUM** | | | |
| 97 | Carbon powder/paste | 5 | Aromatic ring hydrogenation, Hydrogenation of aliphatic carbonyls, Sugar hydrogenation, Selective oxidation |
| 603 | Graphite powder | 5 | Aromatic ring hydrogenation, Hydrogenation of aliphatic carbonyls |
| 619 | Carbon powder/paste | 5 | Aromatic ring hydrogenation, Hydrogenation of aliphatic carbonyls, Sugar hydrogenation, Selective oxidation |
| 620 | Carbon powder/paste | 5 | Aromatic ring hydrogenation, Hydrogenation of aliphatic carbonyls, Sugar hydrogenation, Selective oxidation |
| 622 | Carbon powder/paste | 5 | Glucose hydrogenation |
| 697 | Alumina powder | 5 | Aromatic ring hydrogenation, Hydrogenation of aliphatic carbonyls |
| 698 | Alumina powder | 5 | Aromatic ring hydrogenation, Hydrogenation of aliphatic carbonyls, but especially for bulky molecules |
| 600 | Carbon powder/paste | 5 | Hydrogenation of aldehydes and ketones |
| **MIXED METALS** | | | |
| 120 | Carbon powder/paste | 2.5%Pd, 2.5%Pt | Hydrogenation of nitro groups, Hydrogenation of alkenes |
| 122 | Carbon powder/paste | 2.5%Pd, 2.5%Pt | Hydrogenation of nitro groups, Hydrogenation of alkenes |
| 160 | Carbon powder/paste | 5%Pt, 1.5%Bi | Selective oxidation, Alcohols to carbonyls and acids |
| 161 | Graphite powder | 5%Pt, 1.5%Bi | Selective oxidation |
| 162 | Alumina powder | 5%Pt, 1.5%Bi | Selective oxidation |
| 430 | Carbon powder/paste | 4%Pd, 1%Pt, 3%Bi | Selective oxidation |
| 464 | Carbon powder/paste | 8%Pd, 2%Pt | Selective hydrogenation of nitrate to hydroxylamine |
| 485 | Carbon powder/paste | 4%Pd, 1%Ru | Hydrogenation of nitro groups, Hydrogenation of oximes |
| 610 | Carbon powder/paste | 4.5%Ru, 0.5%Pd | Aromatic ring hydrogenation, Hydrogenation of aliphatic carbonyls |
| 611 | Carbon powder/paste | 5%Ru,0.25%Pd | Aromatic ring hydrogenation, Hydrogenation of aliphatic carbonyls |

**NOTE**

Paste catalysts are free flowing, powder–like materials, containing approximately 50–60% w/w water.
The foregoing lists of catalysts and usually applications are not exhaustive

## PRICAT® **Catalysts**

| **PRICAT** | | | **Metal** | **Support** | **Promotors** | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Powder | Tablet | % | | MgO | $ZrO_2$ | $Cr_2O_3$ | $Al_2O_3$ | MnO |
| NI 52/35 | X | X | 50 | Kieselguhr | X | | X | | |
| NI 55/5 | X | X | 55 | Kieselguhr | X | | | | |
| NI 60/15 | X | X | 60 | Kieselguhr | | X | | X | |
| NI 62/15 | X | | 60 | Kieselguhr | | X | | X | |
| CU 60/8 | | X | 60 | Silica | | | | | |
| CU 60/35 | X | X | 62 | Silica | X | | X | | |
| CO 40/55 | X | X | 40 | Kieselguhr | X | | | | X |

## SPONGE METAL

| **Product** | **Primary Metal** | **Promoters** | **Particle Size, median (u)** | **Typical applications** |
|---|---|---|---|---|
| A-5000 | Nickel | Non-promoted | 33 | General hydrogenation |
| A-5001 | Nickel | Non-promoted | 33 | Standard catalysts at low pH |
| A-5009 | Nickel | Non-promoted | 33 | High clarity and fast filtration rate |
| A-5B00 | Nickel | Non-promoted | 50 | General hydrogenation |
| A-5E09 | Nickel | Non-promoted | 20 | High clarity and high activity |
| A-5F00 | Nickel | Non-promoted | 85 | Fast settlement and fast filtration |
| A-4000 | Nickel | Fe/Cr | 35 | Nitro and nitrile hydrogenation |
| A-4F00 | Nickel | Fe/Cr | 85 | Fast settlement and filtration |
| A-7000 | Nickel | Mo | 35 | High activity after recycling |
| A-7004 | Nickel | Mo | 35 | High activity after recycling |
| A-7200 | Nickel | Mo | 160 | General hydrogenation |
| A-6EB9 | Nickel | Pd | 20 | Significant high activity for hydrogenation |
| A-7063 | Nickel | Mo | 35 | Standard catalyst |
| A-7069 | Nickel | Mo | 35 | Excellent settlement and fast filtration |
| A-7B63 | Nickel | Mo | 50 | Standard catalyst |
| A-7B69 | Nickel | Mo | 50 | Excellent settlement and fast filtration |
| A-7BC9 | Nickel | Mo | 50-65 | Excellent settlement and fast filtration |
| A-7B73 | Nickel | Mo | 30 | Standard catalyst |
| A-2000 | Nickel | Fe | 30 | Nitro group hydrogenation |
| A-3B00 | Copper | Non-promoted | 35 | Dehydrogenation |
| A-8B46 | Cobalt | Fe/Cr | 35 | High selectivity in some applications |
| AMCAT-5 | Nickel | Non-promoted | 35 | Primary amine coated |
| AMCAT-5343 | Nickel | Non-promoted | 35 | Tertiary amine coated |

# 6. Table: Homogeneous Catalysts

Our range of PGM homogeneous catalysts and precursors is listed in the tables below. We have also listed some simple PGM chloride salts which are the starting materials for most co–ordination compounds.

## Solubilities

The relative solubilities of the co–ordination compounds in different solvents are indicated in the tables. For guidance, the following abbreviations have been used:–

| | | |
|---|---|---|
| v.s. | very soluble | *ca.* 1000 g/l |
| s. | soluble | *ca.* 100 g/l |
| f.s. | fairly soluble | *ca.* 15 g/l |
| sl.s. | slightly soluble | *ca.* 10 g/l |
| v.sl.s. | very slightly soluble | *ca.* 1 g/l or less |
| i | insoluble | |

## IRIDIUM COMPOUNDS

| Catalog No. | Compound | Molecular Formula | Empirical Formula |
|---|---|---|---|
| Ir-40 | Carbonylchloro bis(triphenylphosphine) iridium(I)<br>$IrCl(CO)(PPh_3)_2$<br>**Vaska's Complex** | $(CO)ClIr[P(C_6H_5)_3]_2$ | $C_{37}H_{30}ClOP_2Ir$ |
| Ir-42 | Carbonylhydrido tris(triphenylphosphine) iridium(I)<br>$IrH(CO)(PPh_3)_2$ | $(CO)HIr[P(C_6H_5)_3]_3$ | $C_{55}H_{46}OP_3Ir$ |
| Ir–90 | (1,5-cyclooctadiene)pyridine (tricyclohexylphosphine)iridium(I) hexafluorophosphate<br>$[Ir(cod)py(PCy_3)]PF_6$<br>**Crabtree's catalyst** | $[(C_8H_{12})(C_5H_5N)Ir\ P(C_6H_{11})_3]\ PF_6$ | $C_{31}H_{50}F_6NP_2Ir$ |
| Ir–91 | Bis(cyclooctene)di-μ-Chloroiridium(I)<br>$[IrCl(coe)_2]_2$ | $[(C_8H_{14})_2IrCl]_2$ | $C_{16}H_{28}ClIr$ |
| Ir–92 | Bis(1,5-cyclooctadiene)di-μ-methoxodiiridium(I)<br>$[Ir(OMe)(cod)]_2$ | $[(C_8H_{12})Ir(OCH_3)]_2$ | $C_9H_{15}OIr$ |
| Ir–93 | Bis(1,5-cyclooctadiene)di-μ–chlorodiiridium(I)<br>$[IrCl(cod)]_2$ | $[(C_8H_{12})IrCl]_2$ | $C_8H_{12}ClIr$ |
| Ir–113 | Iridium(III) chloride hydrate<br>$[IrCl_3]xH_2O$ | $[IrCl_3]xH_2O$ | – |
| Ir–114 | Chloroiridic acid; Hydrogenhexachloroiridate(IV) hydrate<br>$H_2[IrCl_6]xH_2O$ | $H_2[IrCl_6]xH_2O$ | – |
| Ir-115 | Dichloro(pentamethylcyclopentadienyl)iridium (III) dimer<br>$[Ir(Cp^*)Cl_2]_2$ | $[C_5(CH_3)_5IrCl_2]_2$ | $C_{20}H_{30}Cl_4Ir_2$ |
| Ir–116 | acetylacetonato(1,5-cyclooctadiene)iridium(I)<br>Ir(acac)(cod) | $(C_8H_{12})Ir(CH_3COCHCOCH_3)$ | $C_{13}H_{19}O_2Ir$ |
| Ir–117 | acetylacetonatodicarbonyliridium(I)<br>$Ir(acac)(CO)_2$ | $(CO)_2Ir(CH_3COCHCOCH_3)$ | $C_7H_7O_4Ir$ |
| Ir–118 | Bis(1,5-cyclooctadiene)iridium(I) tetrafluoroborate<br>$[Ir(cod)_2]BF_4$ | $[(C_8H_{12})_2Ir]BF_4$ | $C_{16}H_{24}BF_4Ir$ |

## OSMIUM COMPOUNDS

| Catalog No. | Compound | Molecular Formula | Empirical Formula |
|---|---|---|---|
| Os-100 | Osmium tetroxide<br>Osmium (VIII) oxide<br>$[OsO_4]$ | $OsO_4$ | $OsO_4$ |
| Os-101 | "Potassium osmate dihydrate"<br>Dipotassium trans dioxo tetrahydroxy osmium (VI)<br>$K_2[OsO_2(OH)_4]$ | $K_2[OsO_2(OH)_4]$ | $H_4K_2O_6Os$ |
| FibreCat® 3003 | $OsO_4$ on vinyl pyridine grafted fibers | – | – |
| FibreCat® 3004 | $K_2[OsO_2(OH)_4]$ on triethylamine grafted fibers | – | – |

## IRIDIUM COMPOUNDS

| Color & Form | Mol Wt | % Metal Content | Solubilities | CAS No. (EINECS No.) |
|---|---|---|---|---|
| lemon yellow crystals | 780 | 24.6 | sl.s chloroform sl.s toluene | 14871–41–1<br>2389416 |
| pale yellow crystals | 1008 | 19.1 | sl.s toluene | 17250–25–8 |
| orange crystals | 805 | 23.9 | sl.s acetone, dichloromethane, diethyl ether, ethanol, toluene | 64536–78–3 |
| yellow crystals | 896 | 42.9 | i.water | 12246-51-4 |
| yellow crystals | 663 | 58 | i. water | 12148-71-9 |
| red–orange crystals | 672 | 57.2 | s. chloroform, toluene<br>sl.s acetone, alcohol | 12112–67–3<br>2351707 |
| green-black crystalline flakes | – | 50–56 | f.s alcohol, water | 14996-61-3<br>2330446 |
| black–brown crystals | – | 38–45 | f.s alcohol, water | 16941–92–7<br>2410128 |
| orange crystal | 797 | 48.31 | s. dichloromethane, chloroform | 12354-84-6 |
| yellow crystals | 399 | 48.18 | f.s. dichloromethane, chloroform | 12154-84-6 |
| golden yellow crystals | 347 | 55.39 | s. methanol, acetone, chloroform | 14023-80-4 |
| dark red crystals | 495 | 38.83 | f.s. dichloromethane, chloroform | 35138-23-9 |

## OSMIUM COMPOUNDS

| Color & Form | Mol Wt | % Metal Content | Solubilities | CAS No. (EINECS No.) |
|---|---|---|---|---|
| yellow crystals | 254 | 75 | v.s carbon tetrachloride<br>s. water | 20816–12–0<br>2440587 |
| purple crystals | 368 | 51.6 | s. water | 19718 – 36 – 6 |
| yellow fibers | – | 4–7.5 | i. all known solvents | mixture |
| violet fibers | – | 4–7.5 | i. all known solvents | mixture |

## PALLADIUM COMPOUNDS

| Catalog No. | Compound | Molecular Formula | Empirical Formula |
|---|---|---|---|
| Pd–62 | Bis(acetonitrile) dichloro palladium(II)<br>$PdCl_2(CH_3CN)_2$ | $PdCl_2(CH_3CN)_2$ | $C_4H_6Cl_2N_2Pd$ |
| Pd–63 | Tetrakis(acetonitrile)palladium(II)tetrafluoroborate<br>$[Pd(CH_3CN)_4]\ (BF_4)_2$ | $[Pd(CH_3CN)_4]\ (BF_4)_2$ | $C_8H_{12}B_2F_8N_4Pd$ |
| Pd–70 | Bis(acetylacetonato)palladium(II)<br>$Pd(acac)_2$ | $Pd(CH_3COCHCOCH_3)_2$ | $C_{10}H_{14}O_4Pd$ |
| Pd-91 | Dichloro (norbornadiene) palladium(II)<br>$PdCl_2(nbd)$ | $PdCl_2(C_7H_8)$ | $C_7H_8Cl_2Pd$ |
| Pd-90 | Dichloro(1,5-cyclooctadiene) palladium (II)<br>$PdCl_2(cod)$ | $PdCl_2(C_8H_{12})$ | $C_8H_{12}Cl_2Pd$ |
| Pd–93 | Bis(dibenzylideneacetone)palladium(0)<br>$Pd(dba)_2$ | $Pd[(C_6H_5CH{=}CH)_2CO]_2$ | $C_{34}H_{28}O_2Pd$ |
| Pd–94 | Tris(dibenzylideneacetone)dipalladium(0)<br>$Pd_2(dba)_3$ | $Pd_2[(C_6H_5CH{=}CH)_2CO]_3$ | $C_{51}H_{42}O_3Pd_2$ |
| Pd–95 | Tris(dibenzylideneacetone)dipalladium(0)<br>chloroform adduct<br>$Pd_2(dba)_3xCHCl_3$ | $Pd_2[(C_6H_5CH{=}CH)_2CO]_3CHCl_3$ | $C_{52}H_{43}Cl_3O_3Pd_2$ |
| Pd–100 | *trans* dichloro bis(triphenylphosphine) palladium (II)<br>$PdCl_2(PPh_3)_2$ | $PdCl_2[P(C_6H_5)_3]_2$ | $C_{18}H_{15}Cl_2P_2Pd$ |
| Pd–101 | Tetrakis(triphenylphosphine)palladium(0)<br>$Pd(PPh_3)_4$ | $Pd[P(C_6H_5)_3]_4$ | $C_{72}H_{60}Pd$ |
| Pd–102 | Diacetato[1,3–bis(diphenylphosphino)propane]<br>palladium(II)<br>$Pd(OAc)_2(dppp)$ | $(C_6H_5)_2P(CH_2)_3P(C_6H_5)_2$<br>$Pd(CH_3CO_2)_2$ | $C_{31}H_{32}O_4P_2Pd$ |
| Pd–103 | Dichloro [1,2–bis(diphenylphosphino)ethane]<br>palladium(II)<br>$PdCl_2(dppe)$ | $PdCl_2[(C_6H_5)_2P(CH_2)_2P(C_6H_5)_2]$ | $C_{26}H_{24}Cl_2P_2Pd$ |
| Pd–104 | Diacetatobis(triphenylphosphine)palladium(II)<br>$Pd(OAc)_2(PPh_3)_2$ | $Pd(CH_3CO_2)_2[P(C_6H_5)_3]_2$ | $C_{40}H_{36}O_4P_2Pd$ |
| Pd–105 | Dichloro[1,4–bis(diphenylphosphino)butane]<br>palladium(II)<br>$PdCl_2(dppb)$ | $PdCl_2((C_6H_5)_2P(CH_2)_4P(C_6H_5)_2)$ | $C_{28}H_{28}Cl_2P_2Pd$ |
| Pd–106 | Dichloro [1,1′-bis(diphenylphosphino)ferrocene]<br>palladium(II) dichloromethane adduct<br>$PdCl_2(dppf)\ CH_2Cl_2$ | $PdCl_2[(C_5H_4P(C_6H_5)_2)_2Fe]\ CH_2Cl_2$ | $C_{35}H_{30}Cl_4FeP_2Pd$ |
| Pd–107 | Dichloro [1,1′-bis(diphenylphosphino)ferrocene]<br>palladium(II) acetone adduct<br>$PdCl_2(dppf)\ (CH_3)_2CO$ | $PdCl_2[(C_5H_4P(C_6H_5)_2)_2Fe]\ (CH_3)_2CO$ | $C_{37}H_{34}Cl_2FeOP_2P$ |
| Pd–110 | Di-μ-chlorobis(propenyl) dipalladium (II)<br>Pi Allylpalladium chloride dimer<br>$[PdCl(C_3H_5)]_2$ | $[PdCl(C_3H_5)]_2$ | $C_3H_5ClPd$ |
| Pd–111 | Palladium(II) acetate (exists as trimer)<br>Hexakis(μ–acetato) tripalladium(II)<br>$[Pd(OAc)_2]_3$ | $Pd_3(O_2CCH_3)_6$ | $C_4H_6O_4Pd$ |
| Pd-113 | Di-μ-bromo bis(tri-*t*-butylphosphine)dipalladium (I)<br>$[Pd(\mu\text{-}Br)\mathit{t}\text{-}Bu_3P]_2]$ | $(t\text{-}C_4H_9)_3PPd(\mu\text{-}Br)_2PdP(t\text{-}C_4H_9)_3$ | $C_{12}H_{27}BrPPd$ |
| Pd-114 | *trans*-dichloro bis(tricyclohexylphosphine)<br>palladium(II)<br>$PdCl_2[P(cy)_3]_2$ | $PdCl_2[P(C_6H_{11})_3]_2$ | $C_{36}H_{66}Cl_2P_2Pd$ |
| Pd-115 | *trans*-dichloro bis(tri-o-tolylphosphine)<br>palladium(II)<br>$PdCl_2[P(\mathit{o}\text{-}tol)_3]_2$ | $PdCl_2[P(CH_3C_6H_4)_3]_2$ | $C_{42}H_{42}Cl_2P_2Pd$ |

# PALLADIUM COMPOUNDS

| Color & Form | Mol Wt | % Metal Content | Solubilities | CAS No. (EINECS No.) |
|---|---|---|---|---|
| dark yellow crystals | 259 | 41.0 | s. acetone, chloroform | 14592–56–4<br>2386373 |
| pale yellow crystals | 444 | 23.9 | s. water | 21797-13-7 |
| yellow  orange crystals | 304 | 35.0 | s. chloroform, toluene | 14024–61–4<br>2378598 |
| yellow crystals | 269 | 39.5 | chloroform | 12317-46-3 |
| yellow powder | 286 | 37.3 | sl. s. dichloromethane | 12107-56-1 |
| purple brown crystals | 575 | 18.5 | sls. chloroform | 32005-36-0 |
| dark purple crystals | 916 | 23.2 | s. chloroform | 52409-22-0<br>51364-51-3<br>60748-47-2 |
| purple powder crystals | 1035 | 20.6 | chloroform | 52522-40-4 |
| yellow crystals | 701 | 15.2 | v.sl.s acetone, chloroform | 13965–03–2<br>2377442 |
| yellow crystals | 1154 | 9.4 | s. chloroform, toluene | 14221–01–3<br>2380869 |
| cream crystals | 636 | 16.7 | s. acetic acid, chloroform, methanol<br>sl.s acetone<br>v.sl.s toluene | 149796–59–8 |
| off white crystals | 575 | 18.5 | s. dichloromethane | 19978–61–1 |
| yellow crystals | 749 | 14.2 | insoluble | 14588-08-0 |
| yellow crystals | 603 | 17.6 | sl.s DMF<br>v.sl.s. acetonitrile, water | 29964–62–3 |
| orange-red crystals | 816 | 13.0 | i. water | 95464-05-4 |
| brick red crystals | 789 | 13.4 | s. chloroform<br>sl. s. dichloromethane | 851232-71-8 |
| yellow crystals | 366 | 58.1 | i. water | 12012-95-2 |
| orange-brown crystals | 673 | 47.4 | s. acetic acid, toluene | 3375–31–3<br>2584249 |
| dark green-black crystals | 777 | 27.4 | i. water | 185812-86-6 |
| yellow crystals | 738 | 14.4 | i. water | 29934-17-6 |
| yellow-orange crystals | 786 | 13.5 | i. water | 40691-33-6 |

## PALLADIUM COMPOUNDS – (CONTINUED)

| Catalog No. | Compound | Molecular Formula | Empirical Formula |
|---|---|---|---|
| Pd-116 | Bis(tri-*tert*-butylphosphine)palladium(0)<br>$Pd(t\text{-}Bu_3P)_2$ | $Pd[P(t\text{-}C_4H_9)_3]_2$ | $C_{24}H_{54}P_2Pd$ |
| Pd-117 | Dichloro bis(diphenylphosphinophenyl)ether palladium(II)<br>$PdCl_2$(DPEPhos) | $PdCl_2[[(C_6H_5)_2PC_6H_4]_2O]$ | $C_{36}H_{28}Cl_2OP_2Pd$ |
| Pd-118 | Dichloro [1,1′-bis(di-*tert*-butylphosphino)]ferrocene palladium(II)<br>$PdCl_2$(dtbpf) | $PdCl_2[[(C_4H_9)_2PC_5H_4]_2Fe]$ | $C_{26}H_{44}Cl_2FeP_2Pd$ |
| Pd-119 | Dichloro [1,1′-bis(di-isopropylphosphino)ferrocene] palladium (II)<br>$PdCl_2$(dippf) | $PdCl_2[[(C_3H_7)_2PC_5H_4]_2Fe]$ | $C_{22}H_{36}Cl_2FeP_2Pd$ |
| Pd–120 | Dibromo bis(tri-orthotolylphosphine)palladium(II)<br>$PdBr_2[(o\text{-}tol)_3P]_2$ | $PdBr_2[(CH_3C_6H_4)_3P]_2$ | $C_{21}H_{21}Br_2P_2Pd$ |
| Pd–121 | Dibromo [1,1′-bis(diphenylphosphino)ferrocene] palladium(II)<br>$PdBr_2$(dppf) | $PdBr_2[(C_5H_4P(C_6H_5)_2)_2Fe]$ | $C_{34}H_{28}Br_2FeP_2Pd$ |
| Pd-122 | Dichloro bis(di-*tert*-butylphenylphosphine) palladium (II)<br>$PdCl_2(\ t\text{-}Bu_2Ph\ P)_2$ | $PdCl_2[(C_4H_9)_2C_6H_5P]_2$ | $C_{28}H_{46}Cl_2P_2Pd$ |
| Pd-123 | Dichloro (2,2′-bis(diphenylphosphino) -1,1′-binaphthyly)palladium (II)<br>$PdCl_2$(BINAP) | $PdCl_2[((C_6H_5)_2P)_2C_{20}H_{12}]$ | $C_{44}H_{32}Cl_2P_2Pd$ |
| Pd-124 | Dibromo(2,2′-bis(diphenylphosphino) -1,1′-binaphthyly)palladium (II)<br>$PdBr_2$(BINAP) | $PdBr_2[((C_6H_5)_2P)_2C_{20}H_{12}]$ | $C_{44}H_{32}Br_2P_2Pd$ |
| Pd-125 | Diiodo(2,2′-bis(diphenylphosphino) -1,1′-binaphthyly)palladium (II)<br>$PdI_2$(BINAP) | $PdI_2[((C_6H_5)_2P)_2C_{20}H_{12}]$ | $C_{44}H_{32}I_2P_2Pd$ |
| Pd-126 | Dichloro [(1,3-bis(diphenylphosphino)propane] palladium (II)<br>$PdCl_2$(dppp) | $PdCl_2[(C_6H_5)_2P(CH_2)_3P(C_6H_5)_2]$ | $C_{27}H_{26}Cl_2P_2Pd$ |
| Pd-127 | Dichloro [1,1′-bis(dicyclohexylphosphino) ferrocene]palladium(II)<br>$PdCl_2$(dcypf) | $PdCl_2[[(C_6H_{11})_2PC_5H_4]_2Fe]$ | $C_{34}H_{52}Cl_2FeP_2Pd$ |
| Pd-128 | Dibromo 1,1′-bis[di-*tert*-butylphosphino)ferrocene] palladium(II)<br>$PdBr_2$(dtbpf) | $PdBr_2[[(C_4H_9)_2PC_5H_4]_2Fe]$ | $C_{26}H_{44}Br_2FeP_2Pd$ |
| Pd-130 | Dibromo bis(triphenylphosphine) palladium(II)<br>$PdBr_2(PPh_3)_2$ | $PdBr_2[P(C_6H_5)_3]_2$ | $C_{18}H_{15}P_2Br_2Pd$ |
| Pd-132 | Dichlorobis( p-dimethylamino phenylditbutyl phosphine) palladium(II)<br>$PdCl_2(Amphos)_2$ | $PdCl_2[(CH_3)_2NC_6H_4P(t\text{-}C_4H_9)_2]_2$ | $C_{32}H_{56}Cl_2N_2P_2Pd$ |
| Pd-133 | Dichloro bis(dicyclohexylphosphino)propane palladium(II)<br>$PdCl_2$(dcypp) | $PdCl_2[(C_6H_{11})_2P(CH_2)_3P(C_6H_{11})_2]$ | $C_{27}H_{50}Cl_2P_2Pd$ |
| Pd-134 | Dichloro(9,9-dimethyl-4,5-bis(diphenyl phosphino)xanthene)palladium(II)<br>$PdCl_2$(Xant-Phos) | $PdC_{l2}(C_{39}H_{32}P_2O)$ | $C_{39}H_{32}Cl_2OP_2Pd$ |
| Pd-135 | Dichloro(9,9-Dimethyl-4,5-bis(di-t-butylphosphino) xanthene)palladium(II)<br>$PdCl_2(t\text{-}Bu_2\text{-}Xant\text{-}Phos)$ | $PdCl_2(C_{31}H_{48}P_2O)$ | $C_{31}H_{48}Cl_2OP_2Pd$ |

## PALLADIUM COMPOUNDS – (CONTINUED)

| Color & Form | Mol Wt | % Metal Content | Solubilities | CAS No. (EINECS No.) |
|---|---|---|---|---|
| off white crystals | 510 | 20.9 | i. water (but decomposes) | 53199-31-8 |
| light yellow crystals | 719 | 14.8 | i. water | 205319-06-08 |
| dark red-brown crystals | 651 | 16.3 | i.water | 95408-45-0 |
| orange-red crystals | 595 | 17.8 | i.water | 215788-65-1 |
| orange-yellow crystals | 875 | 12.0 | i.water | 24554-43-6 |
| purple-red crystals | 820 | 12.9 | s. chloroform, dichloromethane | 124268-93-5 |
| yellow crystals | 622 | 17.1 | s. dichloromethane | 34409-44-4 |
| orange crystals | 800 | 13.3 | sl. s. dichloromethane | 253157-79-8 |
| orange crystals | 889 | 12.0 | sl. s. dichloromethane | 366488-99-5 |
| purple crystals | 983 | 10.8 | sl. s. dichloromethane | unassigned |
| pale yellow-white crystals | 590 | 18.0 | s. dichloromethane | 59831-02-6 |
| orange crystals | 756 | 14.1 | sl. s. dichloromethane | 917511-90-1 |
| dark brown crystals | 741 | 14.4 | s. dichloromethane | 1000310-63-3 |
| orange crystals | 791 | 13.5 | v.sl. s. acetone, acetonitrile | 25044-96-6 |
| yellow crystals | 708 | 15.0 | s. dichloromethane | 887919-35-9 |
| white crystals | 614 | 17.3 | sl. s. dichloromethane<br>sl. s chloroform | 1041005-52-0 |
| yellow crystals | 756 | 14.1 | sl. s. dichloromethane | 205319-10-4 |
| red crystals | 676 | 15.7 | sl. s chloroform | not assigned |

## PALLADIUM COMPOUNDS – (CONTINUED)

| Catalog No. | Compound | Molecular Formula | Empirical Formula |
|---|---|---|---|
| Pd-138 | Diiodo [1,1′-bis(di-*tert*-butylphosphino)ferrocene] palladium(II)<br>$PdI_2$(d*t*bpf) | $PdI_2[[(C_4H_9)_2PC_5H_4]_2Fe]$ | $C_{26}H_{44}FeI_2P_2Pd$ |
| Pd-141 | Bis(tri-o-tolylphosphine)palladium(0)<br>$Pd[(o\text{-}tol)_3P]_2$ | $Pd[P(CH_3C_6H_4)_3]_2$ | $C_{42}H_{42}P_2Pd$ |
| Pd-142 | Dibromo(1,5-cyclooctadiene) palladium (II)<br>$PdBr_2$(cod) | $PdBr_2(C_8H_{12})$ | $C_8H_{12}Br_2Pd$ |
| Pd-145 | Dibromo [1, 1′-bis(di-isopropylphosphino)ferrocene] palladium(II)<br>$PdBr_2$(dippf) | $PdBr_2[[(C_3H_7)_2PC_5H_4]_2Fe]$ | $C_{22}H_{36}Br_2FeP_2Pd$ |
| Q Phos | 1,2,3,4,5-Pentaphenyl-1′-(di-tert-butylphosphino) ferrocene<br>(Used in conjunction with Pd precursor) | $[(C_6H_5)_5C_5]Fe[C_5H_4P(C_4H_9)_2]$ | $C_{48}H_{47}FeP$ |

## FIBRECAT®

| Catalog No. | Compound | Molecular Formula |
|---|---|---|
| ***The following catalysts are supported on ploypropylene fibres through the phenyl of the phosphine ligand. FibreCats® are insoluable in all known solvents.*** | | |
| FC-1001 | Diaceto(triphenylphosphine)palladium | |
| FC-1029 | *trans*-dichloro(acetonitrile)(triphenylphosphine)palladium | |
| FC-1030 | (Benzonitrile)(trans-dichloro)(triphenylphosphine)palladium | |
| FC-1031 | (π-allyl)(chloro)(triphenylphosphine)palladium | |
| FC-1032 | *trans*-dichloro(tri-*tert*-butylphosphine)(triphenylphosphine)palladium | |
| FC-1033 | *trans*-dichloro(di-*tert*-butyl(1′,2′,3′,4′,5′-pentaphenylferrocenyl) phosphine)(triphenylphosphine)palladium | |
| FC-1034 | *trans*-dichloro(di-*tert*-butyl(phenyl)phosphine) (triphenylphosphine)palladium | |
| FC-1034A | *trans*-dichloro((*N,N*-dimethyl-anilino)di-*tert*-butylphosphine) (triphenylphosphine)palladium | |
| FC-1035 | *trans*-dichloro(1,1′-Bis(diphenylphosphino)ferrocene) (triphenylphosphine)palladium | |
| FC-1036 | *trans*-dichloro(2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl) (triphenylphosphine)palladium | |
| FC-1037 | *trans*-dichloro(1,1′-Bis(diisopropylphosphino)ferrocene) (triphenylphosphine)palladium | |
| FC-1038 | *trans*-dichloro(1,3-Dihydro-1,3-diisopropyl-4,5-dimethyl-2H-imidazol-2-ylidene)(triphenylphosphine)palladium | |
| FC-1039 | *trans*-dichloro(acetonitrile)(dicyclohexyl(phenyl) phosphine)palladium | |
| FC-1042 | *trans*-dichloro(tri-*tert*-butylphosphine)(di-cyclohexyl (phenyl)phosphine)palladium | |
| FC-1043 | *trans*-dichloro(di-*tert*-butyl(1′,2′,3′,4′,5′-pentaphenyl ferrocenyl)phosphine)(di-cyclohexyl(phenyl)phosphine)palladium | |
| FC-1044 | *trans*-dichloro(di-*tert*-butyl(phenyl)phosphine)(di-cyclohexyl (phenyl)phosphine)palladium | |
| FC-1045 | *trans*-dichloro(1,1′-Bis(diphenylphosphino)ferrocene) (di-cyclohexyl(phenyl)phosphine)palladium | |
| FC-1046 | *trans*-dichloro(2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl) (di-cyclohexyl(phenyl)phosphine)palladium | |
| FC-1047 | *trans*-dichloro(1,1′-Bis(diisopropylphosphino)ferrocene) (di-cyclohexyl(phenyl)phosphine)palladium | |
| FC-1048 | *trans*-dichloro((*N,N*-dimethyl-aniline)di-*tert*-butylphosphine) (di-cyclohexyl(phenyl)phosphine)palladium | |

## PALLADIUM COMPOUNDS – (CONTINUED)

| Color & Form | Mol Wt | % Metal Content | Solubilities | CAS No. (EINECS No.) |
|---|---|---|---|---|
| dark brown crystal | 835 | 12.8 | – | not assigned |
| yellow crystals | 715 | 14.9 | slightly soluble in toluene<br>i. alcohol, water | 69861-71-8 |
| orange powder | 374 | 28.4 | sl. s. dichloromethane | 12145-47-0 |
| red crystals | 685 | 15.5 | s. dichloromethane | not assigned |
| pink-red solid | 711 | – | i. water | 312959-24-3 |

## FIBRECAT)

| Color & Form | % Metal Content | CAS No. (EINECS No.) |
|---|---|---|
| yellow fibre | 6.0 | 457645-05-5 |
| orange fibre | 8-10 | 1005413-19-3 |
| orange fibre | 6-8 | not assigned |
| orange fibre | 6-8 | not assigned |
| yellow fibre | 4-6 | 960620-60-4 |
| brown fibre | 5-7 | 1073550-94-3 |
| orange fibre | 4-6 | 1073551-04-8 |
| yellow fibre | 4-6 | 1073551-14-0 |
| orange fibre | 4-6 | 1073551-09-3 |
| orange fibre | 4-6 | 1073551-11-7 |
| red fibre | 4-6 | 1073551-12-8 |
| red fibre | 6-8 | 1073551-13-9 |
| red fibre | 8-10 | 1073549-97-9 |
| gold fibre | 4-6 | 1073551-16-2 |
| brown fibre | 5-7 | 1073551-18-4 |
| gold fibre | 5-7 | 1073551-20-8 |
| gold fibre | 5-7 | 1073551-23-1 |
| gold fibre | 6-8 | 1073551-49-1 |
| red fibre | 6-8 | 1073552-02-9 |
| gold fibre | 4-6 | 1073552-38-1 |

## PLATINUM COMPOUNDS

| Catalog No. | Compound | Molecular Formula | Empirical Formula |
|---|---|---|---|
| Pt–62 | *Cis*–bis(acetonitrile)dichloroplatinum(II)<br>*Cis*–$PtCl_2(CH_3CN)_2$ | $PtCl_2(CH_3CN)_2$ | $C_4H_6Cl_2N_2Pt$ |
| Pt–70 | Bis(acetylacetonato)platinum(II)<br>$Pt(C_5H_7O_2)_2$ | $Pt(CH_3COCHCOCH_3)_2$ | $C_{10}H_{14}O_4Pt$ |
| Pt–90 | Dichloro ($\eta^4$–norbornadiene)platinum(II)<br>$PtCl_2$(nbd) | $PtCl_2(C_7H_8)$ | $C_7H_8Cl_2Pt$ |
| Pt–91 | (1,5-Cyclooctadiene)diiodoplatinum(II)<br>$PtI_2$(cod) | $PtI_2(C_8H_{12})$ | $C_8H_{12}I_2Pt$ |
| Pt–96 | Dichloro (1,5-Cyclooctadiene)platinum(II)<br>$PtCl_2$(cod) | $PtCl_2(C_8H_{12})$ | $C_8H_{12}Cl_2Pt$ |
| Pt–100 | *Cis*–Dichlorobis(triphenylphosphine) platinum(II)<br>*Cis*–$PtCl_2(PPh_3)_2$ | $PtCl_2[P(C_6H_5)_3]_2$ | $C_{36}H_{30}Cl_2P_2Pt$ |
| Pt–112 | *Cis*- or *trans*–Dichlorobis(diethylsulfide) platinum(II)<br>*Cis*- or *trans*–$PtCl_2(SEt_2)_2$ | $PtCl_2[S(C_2H_5)_2]_2$ | $C_8H_{20}Cl_2PtS_2$ |
| Pt–114 | Karstedt catalyst solution<br>Approximate formula<br>$Pt_2$(divinyltetramethyldisiloxane)$_3$ | $Pt_2(CH_2CH(CH_3)_2SiO$<br>$Si(CH_3)_2CHCH_2)_3$ | $C_{24}H_{54}O_3Pt_2Si_6$ |
| FibreCat®<br>4001 | Chloroplatinic acid on pyridine fibers | | |
| | Platinum(II) chloride<br>$PtCl_2$ | $PtCl_2$ | $Cl_2Pt$ |
| | Chloroplatinic acid; Hydrogen hexachloroplatinate(IV) hydrate<br>$H_2[PtCl_6].H_2O$ | $H_2[PtCl_6]H_2O$ | $H_4Cl_6OPt$ |

## RHODIUM COMPOUNDS

| Catalog No. | Compound | Molecular Formula | Empirical Formula |
|---|---|---|---|
| Rh–40 | Carbonylchloro bis(triphenylphosphine) rhodium(I)<br>$RhCl(CO)(PPh_3)_2$ | $RhCl(CO)(P(C_6H_5)_3)_2$ | $C_{37}H_{30}ClOP_2Rh$ |
| Rh–42 | Carbonyl hydrido tris(triphenylphosphine) rhodium(I)<br>$RhH(CO)(PPh_3)_3$ | $RhH(CO)(P(C_6H_5)_3)_3$ | $C_{55}H_{46}OP_3Rh$ |
| Rh–43 | Acetylacetonatocarbonyltriphenylphosphine rhodium(I)<br>**(ROPAC)**<br>Rh(acac)(CO)$(PPh_3)$ | $Rh(CH_3COCHCOCH_3)$<br>$(CO)P(C_6H_5)_3$ | $C_{24}H_{22}O_3PRh$ |
| Rh–50 | Acetylacetonatodicarbonyl rhodium(I)<br>Rh(acac)$(CO)_2$ | $Rh(CH_3COCHCOCH_3)(CO)_2$ | $C_7H_7O_4Rh$ |
| Rh–70 | Tris(acetylacetonato) rhodium(III)<br>Rh(acac)$_3$ | $Rh(CH_3COCHCOCH_3)_3$ | $C_{15}H_{21}O_6Rh$ |
| Rh–92 | Di-μ–chloro bis(norbornadiene) dirhodium(I)<br>[RhCl(nbd)]$_2$ | $[RhCl(C_7H_8]_2$ | $C_7H_8ClRh$ |
| Rh–93 | Di-μ–chloro bis(1,5-cyclooctadiene) dirhodium(I)<br>[RhCl(cod)]$_2$ | $[RhCl(C_8H_{12})]_2$ | $C_8H_{12}ClRh$ |
| Rh–95 | Acetylacetonato(1,5-cyclooctadiene)rhodium(I)<br>Rh(acac)(cod) | $Rh(C_8H_{12})(CH_3COCHCOCH_3)$ | $C_{13}H_{19}O_2Rh$ |

## PLATINUM COMPOUNDS

| Color & Form | Mol Wt | % Metal Content | Solubilities | CAS No. (EINECS No.) |
|---|---|---|---|---|
| pale yellow crystals | 348 | 56 | v.sl.s acetone<br>i. dichloromethane<br>sl.s. DMF | 13869–38–0<br>2376192 |
| lemon needles | 393 | 49.6 | v.s chloroform | 15170–57–7<br>2392235 |
| cream crystals | 358 | 54.4 | s. acetic acid | 12152–26–0<br>2352716 |
| yellow crystals | 557 | 35 | s. dichloromethane | 12266–72–7<br>2355387 |
| pale yellow crystals | 374 | 52.1 | sl.s. chloroform, dichloromethane<br>v.sl.s. alcohols | 12080–32–9<br>2351445 |
| white crystals | 790 | 24.7 | v.sl.s. chloroform, hexane, toluene | 15604-36-1<br>2334959 |
| bright yellow crystals | 446 | 43.7 | v.s acetone<br>s. ethyl acetate | 15337–84–5<br>2393731 |
| pale yellow solution | 949 | 3 – 4 | dictated by solvent used | 68478–92–2<br>2708444 |
| orange fibers |  | 3.5-6.0 | i. all known solvents | not assigned |
| olive green crystals | 266 | 72.8–73.6 | v.sl.s acetone, alcohol, water | 10025–65–7<br>2330341 |
| orange–red crystals |  | 39–42 | v.s acetone, alcohol, ether, ethyl acetate, water | 16941–12–1<br>2410107 |

## RHODIUM COMPOUNDS

| Color & Form | Mol Wt | % Metal Content | Solubilities | CAS No. (EINECS No.) |
|---|---|---|---|---|
| yellow crystals | 691 | 14.9 | f.s chloroform, ethanol | 13938–94–8<br>2377128 |
| yellow crystals | 918 | 11.2 | f.s chloroform | 17185–29–4<br>2412303 |
| yellow crystals | 492 | 20.9 | s. chloroform<br>f.s toluene | 25470–96–6<br>2470150 |
| green flakey crystals<br>dichroic pink | 258 | 39.9 | s. acetone<br>sl.s alcohol, chloroform, toluene | 14874–82–9<br>2389479 |
| yellow crystals | 400 | 25.8 | v.s chloroform<br>s. alcohol | 14284–92–5<br>2381925 |
| yellow crystals | 461 | 44.7 | v.sl.s most solvents | 12257–42–0<br>2355104 |
| orange crystals | 493 | 41.8 | sl.s acetone, methanol<br>s. chloroform | 12092–47–6<br>2351576 |
| orange crystals | 310 | 33.0 | s. sl. chloroform | 12245-39-5 |

## RHODIUM COMPOUNDS – (CONTINUED)

| Catalog No. | Compound | Molecular Formula | Empirical Formula |
|---|---|---|---|
| Rh-96 | Bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate<br>$[Rh(cod)_2]\ BF_4$ | $[Rh(C_8H_{12})_2]\ BF_4$ | $C_{16}H_{24}BF_4Rh$ |
| Rh–97 | Bis(norbornadiene)rhodium(I) tetrafluoroborate<br>$[Rh(nbd)_2]\ BF_4$ | $[Rh(C_7H_8)_2]\ BF_4$ | $C_{14}H_{16}BF_4Rh$ |
| Rh–98 | Bis(1,5-cyclooctadiene)rhodium(I)trifluoromethanesulfonate<br>$[Rh(cod)_2]\ CF_3SO_3$ | $[Rh(C_8H_{12})_2]\ CF_3SO_3$ | $C_{17}H_{24}F_3O_3RhS$ |
| Rh–100 | Chloro tris(triphenylphosphine)rhodium(I)<br>$RhCl(PPh_3)_3$<br>**Wilkinson's catalyst** | $RhCl[P(C_6H_5)_3]_3$ | $C_{54}H_{45}ClP_3Rh$ |
| Rh–101 | Bromo tris(triphenylphosphine)rhodium(I)<br>$RhBr(PPh_3)_3$ | $RhBr[P(C_6H_5)_3]_3$ | $C_{54}H_{45}BrP_3Rh$ |
| Rh–105 | Hydrido tetrakis(triphenylphosphine)rhodium(I)<br>$RhH(PPh_3)_4$ | $RhH[P(C_6H_5)_3P]_4$ | $C_{72}H_{61}P_4Rh$ |
| Rh–110 | Rhodium(II) acetate dimer<br>Rhodium(II) acetate "Green"<br>$[Rh(OAc)_2]_2$ | $[Rh(O_2CCH_3)_2]_2$ | $C_4H_6O_4Rh$ |
| Rh–112 | "Rhodium(III) acetate"<br>Hexa(acetato) $\mu_3$–oxo tris(aquo)<br>trirhodium acetate<br>$[Rh_3(OAc)_6–\mu_3–O(H_2O)_3]OAc$ | $[Rh_3(OAc)_6–\mu_3–O(H_2O)_3]OAc$ | $C_{14}H_{27}O_{17}Rh_3$ |
| Rh–115 | Rhodium(II) octanoate dimer<br>$[Rh(C_8H_{15}O_2)_2]_2$ | $[Rh(O_2C(CH_2)_6CH_3)_2]_2$ | $C_{16}H_{30}O_4Rh$ |
| Rh-116 | Rhodium(II)trifluoroacetate dimer<br>$[Rh(tfa)_2]_2$ | $[Rh(CF_3CO_2)_2]_2$ | $C_4F_6O_4Rh$ |
| Rh–120 | Di $\mu$–chloro dichloro bis(pentamethylcyclopentadiene)<br>dirhodium (III)<br>$[RhCl_2Cp^*]_2$ | $[RhCl_2[C_5(CH_3)_5]]_2$ | $C_{10}H_{15}Cl_2Rh$ |
| Rh–125 | Bis(norbornadiene)rhodium(I)trifluoromethanesulfonate<br>$[Rh(nbd)_2]\ CF_3SO_3$ | $[Rh(C_7H_8)_2]CF_3SO_3$ | $C_{15}H_{16}F_3O_3RhS$ |
| Rh–126 | Acetylacetoatobisethylene rhodium(I)<br>$Rh(acac)(C_2H_4)_2$ | $(CH_3COCHCOCH_3)Rh(C_2H_4)_2$ | $C_9H_{15}O_2Rh$ |
| Rh–127 | Acetylacetoatonorbornadiene rhodium(I)<br>Rh(acac)(nbd) | $Rh(CH_3COCHCOCH_3)(C_7H_8)$ | $C_{12}H_{15}O_2Rh$ |
| Rh-128 | Bis(1,5-cyclooctadiene)rhodium(I) hexafluoroantimonate<br>$[Rh(cod)_2]\ SbF_6$ | $[Rh(C_8H_{12})_2]SbF_6$ | $C_{16}H_{24}F_6RhSb$ |
| Rh-129 | (1,5-cyclooctadiene)pentamethylcyclopentadiene rhodium(I)<br>$[RhCp^*(cod)]$ | $Rh[C_5(CH_3)_5](C_8H_{12})$ | $C_{18}H_{27}Rh$ |
| Rh-130 | 1, 1′-Bis(di-cyclohexylphosphino)ferrocene<br>(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate<br>$[Rh\ (dcypf)(cod)]BF_4$ | $[[(C_6H_{11})_2PC_5H_4]_2Fe]Rh(C_8H_{12})]\ BF_4$ | $C_{42}H_{64}BFeF_4P_2Rh$ |
| Rh-131 | 1, 1′-Bis(di-cyclohexylphosphino)ferrocene<br>(norbornadiene)rhodium(I) tetrafluoroborate<br>$[Rh\ (dcypf)(nbd)]BF_4$ | $[[(C_6H_{11})_2PC_5H_4]_2Fe]Rh(C_7H_8)]\ BF_4$ | $C_{41}H_{60}BFeF_4P_2Rh$ |
| Rh-132 | 1, 1′-Bis(di-iso-propylphosphino)ferrocene<br>(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate<br>$[Rh\ (dippf)(cod)]BF_4$ | $[[(C_3H_7)_2PC_5H_4]_2Fe]Rh(C_8H_{12})]\ BF_4$ | $C_{30}H_{48}BFeF_4P_2Rh$ |
| Rh-133 | 1, 1′-Bis(di-iso-propylphosphino)ferrocene<br>(norbornadiene)rhodium(I) tetrafluoroborate<br>$[Rh\ (d\mathit{i}ppf)(nbd)]BF_4$ | $[[(C_3H_7)_2PC_5H_4]_2Fe]Rh(C_7H_8)]\ BF_4$ | $C_{29}H_{44}BFeF_4P_2Rh$ |
| Rh-134 | 1, 1′-Bis(diphenylphosphino)ferrocene<br>(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate<br>$[Rh\ (dppf)(cod)]BF_4$ | $[[(C_6H_5)_2PC_5H_4]_2Fe]Rh(C_8H_{12})]\ BF_4$ | $C_{42}H_{40}BFeF_4P_2Rh$ |

## RHODIUM COMPOUNDS – (CONTINUED)

| Color & Form | Mol Wt | % Metal Content | Solubilities | CAS No. (EINECS No.) |
|---|---|---|---|---|
| red-brown crystals | 406 | 25.3 | sl. s. methyl ethyl ketone, dichloromethane | 35138-22-8 |
| dark red crystals | 374 | 27.5 | f.s. dichloromethane | 36620–11–8 |
| dark red crystals | 468 | 22.0 | s. chloroform | 99326-34-8 |
| magenta crystals | 925 | 11.1 | v.s chloroform<br>sl.s acetone, alcohol<br>v.sl.s diethyl ether, toluene | 14694–95–2<br>2387445 |
| orange crystals | 970 | 10.6 | v.s. chloroform<br>sl.s acetone, alcohol<br>v.sl.s diethyl ether, toluene | 14973–89–8<br>2390505 |
| yellow crystals | 1153 | 8.9 | s. chloroform, toluene | 18284–36–1 |
| green crystals | 442 | 46.6 | sl.s methanol v.sl.s acetone, acetic acid, chloroform, water | 15956–28–2<br>2400848 |
| available as solution | 570 | 34–39 | s. acetic acid, water | 42204–14–8<br>2557079 |
| green crystals | 779 | 26.4 | sl.s alcohol | 73482–96–9 |
| green crystals | 658 | 31.3 | insoluble in water | 31126-95-1 |
| burgundy crystals | 618 | 33.3 | s. chloroform, acetone<br>sl.s. THF, methanol<br>i. diethyl ether | 12354–85–7 |
| orange crystals | 436 | 23.6 | s. dichloromethane & chloroform | 178397-71-2 |
| yellow crystals | 258 | 39.9 | s. dichloromethane & chloroform | 12082-47-2 |
| yellow crystals | 294 | 34.9 | s. dichloromethane & chloroform | 32354-50-0 |
| brown crystals | 555 | 18.5 | f.s. dichloromethane | 130296-28-5 |
|  | 346 | 29.7 | – | 55787-63-8 |
| orange crystals | 876 | 11.7 | s. sl. chloroform<br>s. sl. dichloromethane | not assigned |
| orange crystals | 860 | 12.0 | s. sl. chloroform<br>s. sl. dichloromethane | not assigned |
| orange crystals | 716 | 14.4 | s. sl. chloroform<br>s. sl. dichloromethane | 157772-65-1 |
| orange crystals | 700 | 14.4 | s. sl. chloroform<br>s. sl. dichloromethane | not assigned |
| orange crystals | 852 | 12.1 | s. sl. chloroform<br>s. sl. dichloromethane | not assigned |

## RHODIUM COMPOUNDS – (CONTINUED)

| Catalog No. | Compound | Molecular Formula | Empirical Formula |
|---|---|---|---|
| Rh-135 | 1, 1′-Bis(diphenylphosphino)ferrocene (norbornadiene)rhodium(I) tetrafluoroborate<br>[Rh (dppf)(nbd)]$BF_4$ | $[[(C_6H_5)_2PC_5H_4]_2Fe]Rh(C_7H_8)]\ BF_4$ | $C_{41}H_{36}BFeF_4P_2Rh$ |
| Rh-136 | 1, 1′-Bis(di-*tert*-butylphosphino)ferrocene (norbornadiene)rhodium(I) tetrafluoroborate<br>[Rh (d*t*bpf)(nbd)]$BF_4$ | $[[(C_4H_9)_2PC_5H_4]_2Fe]Rh(C_7H_8)]\ BF_4$ | $C_{32}H_{48}BFeF_4P_2Rh$ |
| Rh-137 | 1,4-Bis(diphenylphosphino)butane (1,5-cyclooctadiene)rhodium(I) tetrafluoroborate<br>[Rh (dppb)(cod)]$BF_4$ | $[[(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2]Rh(C_8H_{12})]\ BF_4$ | $C_{36}H_{40}BF_4P_2Rh$ |
| Rh-138 | 1,4-Bis(diphenylphosphino)butane (norbornadiene)rhodium(I) tetrafluoroborate<br>[Rh (dppb)(nbd)]$BF_4$ | $[[(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2]Rh(C_7H_8)]\ BF_4$ | $C_{35}H_{36}BF_4P_2Rh$ |
| Rh-139 | Rhodium (2–ethylhexanoate) dimer in 2–ethyl hexanol<br>$[Rh(C_7H_{15}CO_2)_2]_2$ | $Rh_2(CH_3(CH_2)_3CH(CH_2CH_3)CO_2)_4$ | $C_{16}H_{30}O_4Rh$ |
| Rh-140 | Rhodium(III) chloride hydrate<br>$RhCl_3nH_2O$ | $[RhCl_3]nH_2O$ | - |
|  | Rhodium(III) iodide<br>$RhI_3$ | $RhI_3$ | $RhI_3$ |
| FibreCat® 2006 | $[Rh(nbd)Cl]_2$ on triphenylphosphine grafted fibers | – | – |

## RHODIUM COMPOUNDS

| Color & Form | Mol Wt | % Metal Content | Solubilities | CAS No. (EINECS No.) |
|---|---|---|---|---|
| orange crystals | 836 | 12.3 | s. sl. chloroform<br>s. sl. dichloromethane | not assigned |
| orange crystals | 740 | 13.6 | s. sl. chloroform<br>s. sl. dichloromethane | not assigned |
| orange crystals | 724 | 14.2 | s. sl. chloroform<br>s. sl. dichloromethane | 79255-71-3 |
| orange crystals | 708 | 14.5 | s. sl. chloroform<br>s. sl. dichloromethane | not assigned |
| green crystals | 778 | 26.4 | sl. s. Ethanol | 73482-96-9 |
| dark red flakes | – | 39–43 | s. alcohol, water<br>sl.s acetone | 20765–98–4 *<br>2331654 |
| black crystals | 484 | 21.3 | i. most solvents | 15492–38–3<br>2395215 |
| yellow fibers |  | 2.0-3.5 | i. all known solvents | not assigned |

# RUTHENIUM COMPOUNDS

| Catalog No. | Compound | Molecular Formula | Empirical Formula |
|---|---|---|---|
| Ru–41 | Dicarbonyldichlorobis (triphenylphosphine)ruthenium(II)<br>$RuCl_2(CO)_2(PPh_3)_2$ | $(CO)_2RuCl_2[P(C_6H_5)_3]_2$ | $C_{38}H_{30}O_2Cl_2P_2Ru$ |
| Ru–42 | Carbonylchlorohydrido tris(triphenylphosphine) ruthenium(II)<br>$RuClH(CO)(PPh_3)_3$ | $[(C_6H_5)_3P]_3HRuCl(CO)$ | $C_{55}H_{46}OClP_3Ru$ |
| Ru–70 | Tris(2,4-pentanedionato)ruthenium(III)<br>Tris(acetylacetonato) ruthenium(III)<br>$Ru(acac)_3$ | $Ru(CH_3COCHCOCH_3)_3$ | $C_{15}H_{21}O_6Ru$ |
| Ru–90 | Dichloro (1,5-cyclooctadiene) ruthenium(II) polymer<br>$[RuCl_2(cod)]n$ | $[(C_8H_{12})RuCl_2]_n$ | $C_8H_{12}Cl_2Ru$ |
| Ru–92 | (1,5 cyclooctadiene)bistrifluoroacetato ruthenium(II) dimer<br>$[Ru(tfa)_2(cod)]_2$ | $[(C_8H_{12})Ru(CF_3CO_2)_2]_2$ | $C_{12}H_{12}F_6O_4Ru$ |
| Ru–100 | Dichloro tris(triphenylphosphine)ruthenium(II)<br>$RuCl_2(PPh_3)_3$ | $RuCl_2[P(C_6H_5)_3P]_3$ | $C_{54}H_{45}Cl_2P_3Ru$ |
| Ru–120 | Dichloro-di-μ-chloro bis (p–cymene) diruthenium(II)<br>Dichloro(p-cymene)ruthenium(II) dimer<br>$[RuCl_2(C_{10}H_{14})]_2$ | $[(CH_3C_6H_4C_3H_7)RuCl_2]_2$ | $C_{10}H_{14}Cl_2Ru$ |
| Ru–121 | Diiodo-di-μ-iodo bis (p–cymene) diruthenium(II)<br>Diiodo(p-cymene)ruthenium(II) dimer<br>$[RuI_2(C_{10}H_{14})]_2$ | $[(CH_3C_6H_4C_3H_7)RuI_2]_2$ | $C_{10}H_{14}I_2Ru$ |
| Ru-122 | Dichloro-di-μ-chloro bis (mesitylene) diruthenium(II)<br>Dichloro(mesitylene)ruthenium(II) dimer<br>$[RuCl_2(mesitylene)]_2$ | $[(CH_3)_3C_6H_3)RuCl_2]_2$ | $C_9H_{12}Cl_2Ru$ |
| Ru-123 | Dichloro-di-μ-chloro bis (benzene) diruthenium(II)<br>Dichloro(benzene)ruthenium(II) dimer<br>$[RuCl_2(Benzene)]_2$ | $[(C_6H_6)RuCl_2]_2$ | $C_6H_6Cl_2Ru$ |
| Ru-124 | Bis(2-methylallyl)(1,5-cyclooctadiene)ruthenium (II)<br>$Ru(C_4H_7)_2(cod)$<br>$Ru(methylallyl)_2(cod)$ | $(C_8H_{12})Ru(CH_2C(CH_3)CH_2)_2$ | $C_{16}H_{26}Ru$ |
| Ru–130 | Tetra (n–propylammonium)perruthenate , TPAP<br>$[NPr_4][RuO_4]$ | $[(C_3H_7)_4N]RuO_4$ | $C_{12}H_{28}NO_4Ru$ |
| Ru-131 | Ruthenium(III) chloride hydrate<br>$[RuCl_3]xH_2O$ | $[RuCl_3]xH_2O$ | $[RuCl_3]xH_2O$ |
| Ru-132 | Dichloro(pentamethylcyclopentadienyl) ruthenium(III) polymer<br>$(RuCl_2Cp^*)n$ | $[((CH_3)_5C_5)RuCl_2]n$ | $C_{10}H_{15}Cl_2Ru$ |
| Ru-133 | Chloro(pentamethylcyclopentadienyl)(1, 5 cyclooctadiene) ruthenium(II)<br>$RuCl(cod)Cp^*$ | $(C_8H_{12})RuCl(C_5(CH_3)_5)$ | $C_{18}H_{27}ClRu$ |
| Ru-134 | Chloro(cyclopentadienyl)bis(triphenylphosphine) ruthenium(II) ethanol adduct<br>$RuClCp(PPh_3)_2\ C_2H_5OH$ | $CpRuCl[P(C_6H_5)_3]_2\ .C_2H_5OH$ | $C_{43}H_{41}P_2ClORu$ |
| Ru-135 | Chloro(pentamethylcyclopentadienyl) [bis(triphenylphosphine)] ruthenium(II)<br>$RuClCp^*(PPh_3)_2$ | $[C_5(CH_3)_5]RuCl[P(C_6H_5)_3]_2$ | $C_{46}H_{45}ClP_2Ru$ |
| FibreCat® 3002 | $Na_2RuO_4$ on triethylamine grafted fibers | | |

## RUTHENIUM COMPOUNDS

| Color & Form | Mol Wt | % Metal Content | Solubilities | CAS No. (EINECS No.) |
|---|---|---|---|---|
| white crystals | 752 | 13.4 | v.sl.s acetone<br>chloroform, toluene | 14564–35–3<br>2386059 |
| cream white crystals | 952 | 10.6 | i. in most solvents | 16971–33–8<br>2410510 |
| dark red–brown crystals | 398 | 25.4 | s. chloroform<br>sl.s acetone, ethyl acetate<br>methanol,<br>toluene, water | 14284–93–6<br>2381930 |
| dark brown crystals | 280 | 36.1 | i. most solvents | 50982–13–3<br>50982–12–2 |
| yellow crystals | 870 | 23.2 | s. chloroform | 133873-70-8 |
| black crystals | 959 | 10.5 | v.sl.s acetone,<br>alcohol, chloroform,<br>ethyl acetate, toluene | 15529–49–4<br>2395697 |
| dark red crystals | 612 | 33 | s. alcohol, chloroform | 52462–29–0 |
| yellow-brown crystals | 978 | 20.7 | s. chloroform<br>s. dichloromethane | 90614-07-6 |
| red-brown crystals | 584 | 34.6 | s. sl. in DMSO | 52462-31-4 |
| orange-brown crystals | 500 | 40.4 | s. sl. in DMSO | 37366-09-9 |
| off white crystals | 319 | 31.7 | i. water | 12289-94-0 |
| very dark green-brown crystals | 351 | 28.8 | s. acetonitrile<br>s. dichloromethane | 114615–82–6 |
| black crystals | – | 38–43 | s. acetone, alcohol<br>sl.s ethyl acetate | 14898–67–0<br>2331675 |
| red-brown crystals | 307 | 32.9 | i. water | 96503-27-4 |
| yellow-brown crystals | 380 | 26.6 | i. water | 92390-26-6 |
| orange crystals | 772 | 13.09 | s. chloroform, toluene<br>i. alcohol, water | 32993-05-8 |
| yellow crystals | 796 | 12.7 | s. chloroform, toluene | 92361-49-4 |
| grey-black fibers | | 3.0-4.5 | i. all known solvents | |

## GOLD COMPOUNDS

| Catalog No. | Compound | Molecular Formula | Empirical Formula |
|---|---|---|---|
| Au-100 | Chloro(triphenylphosphine)gold(I)<br>AuCl(PPh$_3$) | AuClP(C$_6$H$_5$)$_3$ | $C_{18}H_{16}AuClP$ |
| Au-101 | Chloro(tri-ortho-tolylphosphine)gold(I)<br>AuCl[P(*o*-tol)$_3$] | AuClP(CH$_3$C$_6$H$_4$)$_3$ | $C_{21}H_{21}AuClP$ |
| Au-102 | Chloro(triethylphosphine)gold(I)<br>AuCl(PEt$_3$) | AuClP(C$_2$H$_5$)$_3$ | $C_6H_{15}AuClP$ |

## NICKEL COMPOUNDS

| Catalog No. | Compound | Molecular Formula | Empirical Formula |
|---|---|---|---|
| Ni-103 | Dichloro(1,2-bis(diphenylphosphino)ethane) nickel (II)<br>NiCl$_2$(dppe) | $NiCl_2[(C_6H_5)_2P(CH_2)_2P(C_6H_5)_2P]$ | $C_{36}H_{30}Cl_2NiP_2$ |
| Ni-107 | Dichloro(1,1′-bis(diphenylphosphino)ferrocene) nickel (II)<br>NiCl$_2$(dppf) | $NiCl_2[(C_5H_4P(C_6H_5)_2)_2Fe]$ | $C_{34}H_{28}Cl_2FeNiP_2$ |
| Ni-119 | Dichloro[1,1′-bis(di-isopropylphosphino)ferrocene] nickel (II)<br>NiCl$_2$(d*i*ppf) | $NiCl_2[(C_5H_4P(C_3H_7)_2)_2Fe]$ | $C_{22}H_{36}Cl_2FeNiP_2$ |
| Ni-126 | Dichloro (1,3-bis(diphenylphosphino)propane nickel (II)<br>NiCl$_2$(dppp) | $NiCl_2[(C_6H_5)_2P(CH_2)_3P(C_6H_5)_2]$ | $C_{27}H_{26}Cl_2NiP_2$ |
| Ni-127 | Dichloro[1,1′-bis(di-cyclohexylphosphino)ferrocene] nickel (II)<br>NiCl$_2$(dcpf) | $NiCl_2[(C_5H_4P(C_6H_{11})_2)_2Fe]$ | $C_{34}H_{52}Cl_2FeNiP_2$ |

## GOLD COMPOUNDS

| Color & Form | Mol Wt | % Metal Content | Solubilities | CAS No. (EINECS No.) |
|---|---|---|---|---|
| yellow-white crystals | 495 | 39.8 | s. dichloromethane | 14243-64-2 |
| yellow-white crystals | 537 | 36.7 | s. dichloromethane | 83076-07-7 |
| white crystals | 351 | 56.2 | sl. s. 2-propanol | 15529-90-5 |

## NICKEL COMPOUNDS

| Color & Form | Mol Wt | % Metal Content | Solubilities | CAS No. (EINECS No.) |
|---|---|---|---|---|
| orange crystals | 528 | 11.11 | s. dichloromethane | 14647-23-5 |
| green crystals | 684 | 8.58 | s. dichloromethane | 67292-34-6 |
| green crystals | 548 | 10.71 | s. dichloromethane | not assigned |
| deep red crystals | 542 | 10.83 | s. dichloromethane | 15629-92-2 |
| green crystals | 708 | 8.29 | i. dichloromethane, water | not assigned |

# 7. Table: Chiral Homogeneous Catalysts

| Compound | CAS Numbers | JM Name | Formula |
|---|---|---|---|
| (R)-Xyl-P-Phos $RuCl_2$ (R,R)-Dpen | 832117-84-7 and 478308-93-9 | C1-402 | $C_{60}H_{66}Cl_2N_4O_4P_2Ru$ |
| (S)-Xyl-P-Phos $RuCl_2$ (S,S)-Dpen | 821793-37-7 and 934671-59-7 | C1-412 | $C_{60}H_{66}Cl_2N_4O_4P_2Ru$ |
| (R)-Xyl-PPhos $RuCl_2$ (R)-Daipen | 918130-21-9 | C1-602 | $C_{65}H_{76}Cl_2N_4O_6P_2Ru$ |
| (S)-Xyl-PPhos $RuCl_2$ (S)-Daipen | 918129-65-4 | C1-612 | $C_{65}H_{76}Cl_2N_4O_6P_2Ru$ |
| (R)-BINAP $RuCl_2$ (R)-Daipen | 329735-86-6 | C1-620 | $C_{63}H_{58}Cl_2N_2O_2P_2Ru$ |
| (S)-BINAP $RuCl_2$ (S)-Daipen | 212143-24-3 | C1-630 | $C_{63}H_{58}Cl_2N_2O_2P_2Ru$ |
| (R)-TolBINAP $RuCl_2$ (R)-Daipen | 212210-90-7 | C1-621 | $C_{67}H_{66}Cl_2N_4O_2P_2Ru$ |
| (S)-TolBINAP $RuCl_2$ (S)-Daipen | 212143-26-5 | C1-631 | $C_{67}H_{66}Cl_2N_4O_2P_2Ru$ |
| (R)-PPhos $RuCl_2$ (R,R)-Dpen | 478308-91-7 | C1-400 | $C_{52}H_{50}Cl_2N_4O_4P_2Ru$ |
| (S)-PPhos $RuCl_2$ (S,S)-Dpen | 821793-36-6 | C1-410 | $C_{52}H_{50}Cl_2N_4O_4P_2Ru$ |
| (R)-PPhos $RuCl_2$ (R)-Daipen | 1036379-67-5 | C1-600 | $C_{57}H_{60}Cl_2N_4O_6P_2Ru$ |
| (S)-PPhos $RuCl_2$ (S)-Daipen | – | C1-610 | $C_{57}H_{60}Cl_2N_4O_6P_2Ru$ |
| (R)-Xyl-P-Phos $RuCl_2$ (S,S)-Dpen | – | C1-452 | $C_{60}H_{66}Cl_2N_4O_4P_2Ru$ |
| (S)-Xyl-P-Phos $RuCl_2$ (R,R)-Dpen | 916826-81-8 | C1-462 | $C_{60}H_{66}Cl_2N_4O_4P_2Ru$ |
| (R)-Xyl-PPhos $RuCl_2$ (S)-Daipen | – | C1-652 | $C_{65}H_{76}Cl_2N_4O_6P_2Ru$ |
| (S)-Xyl-PPhos $RuCl_2$ (R)-Daipen | – | C1-662 | $C_{65}H_{76}Cl_2N_4O_6P_2Ru$ |
| (R)-BINAP $RuCl_2$ (S)-Daipen | – | C1-670 | $C_{63}H_{58}Cl_2N_2O_2P_2Ru$ |
| (S)-BINAP $RuCl_2$ (R)-Daipen | – | C1-690 | $C_{63}H_{58}Cl_2N_2O_2P_2Ru$ |
| [(R)-PPhos $RuCl_2$ (S,S)-Dpen] | – | C1-450 | $C_{52}H_{50}Cl_2N_4O_4P_2Ru$ |
| [(S)-PPhos $RuCl_2$ (R,R)-Dpen] | 916826-86-3 | C1-460 | $C_{52}H_{50}Cl_2N_4O_4P_2Ru$ |
| (R)-PPhos $RuCl_2$ (S)-Daipen | – | C1-650 | $C_{57}H_{60}Cl_2N_4O_6P_2Ru$ |
| (S)-PPhos $RuCl_2$ (R)-Daipen | – | C1-680 | $C_{57}H_{60}Cl_2N_4O_6P_2Ru$ |
| [(R,R)-TsDpen-Ru(p-cymene)Cl] | 192139-92-7 | C1-000 | $C_{31}H_{35}ClN_2O_2RuS$ |
| [(S,S)-TsDpen-Ru(p-cymene)Cl] | 192139-90-5 | C1-010 | $C_{31}H_{35}ClN_2O_2RuS$ |
| [(R,R)-MsDpen-Ru(p-cymene)Cl] | 1097730-63-6 and 300664-92-0 | C1-001 | $C_{25}H_{31}ClN_2O_2RuS$ |
| [(S,S)-MsDpen-Ru(p-cymene)Cl] | 925941-93-1 and 329371-25-7 | C1-011 | $C_{25}H_{31}ClN_2O_2RuS$ |
| [(R,R)-TsDpen-Ru(mesitylene)Cl] | 174813-82-2 | C1-020 | $C_{30}H_{33}ClN_2O_2RuS$ |
| [(S,S)-TsDpen-Ru(mesitylene)Cl] | 174813-81-1 and 188753-47-1 | C1-030 | $C_{30}H_{33}ClN_2O_2RuS$ |
| [(R,R)-MsDpen-Ru(mesitylene)Cl] | 1160707-20-9 | C1-021 | $C_{24}H_{28}ClN_2O_2RuS$ |
| [(S,S)-MsDpen-Ru(mesitylene)Cl] | 300664-99-7 and 865488-44-4 | C1-031 | $C_{24}H_{28}ClN_2O_2RuS$ |
| [(R,R)-TsDACH Ru Cl (p-cymene)] | 213603-12-4 | C1-100 | $C_{23}H_{33}ClN_2O_2RuS$ |
| [(S,S)-TsDACH Ru Cl (p-cymene)] | 192057-12-8 | C1-110 | $C_{23}H_{33}ClN_2O_2RuS$ |
| [(R,R)-teth-TsDpen-RuCl] | – | C1-300 | $C_{30}H_{33}ClN_2O_2RuS$ |
| [(S,S)-teth-TsDpen-RuCl] | 851051-43-9 | C1-310 | $C_{30}H_{33}ClN_2O_2RuS$ |
| (R)-PPhos | 221012-82-4 | C4-000 | $C_{30}H_{34}N_2O_4P_2$ |
| (S)-PPhos | 362524-23-0 | C4-020 | $C_{30}H_{34}N_2O_4P_2$ |
| (R)-XylPPhos | 442905-33-1 | C4-002 | $C_{46}H_{50}N_2O_4P_2$ |
| (S)-XylPPhos | 443347-10-2 | C4-022 | $C_{46}H_{50}N_2O_4P_2$ |

## CHIRAL HOMOGENOUS CATALYSTS – (CONTINUED)

| Mol Wt | Color (Solid) | Selected Applications (prec. = precursor) | Metal Content |
|---|---|---|---|
| 1141.11 | Yellow | Noyori technology -Ketone hydrogenation | 8.86% |
| 1141.11 | Yellow | Noyori technology -Ketone hydrogenation | 8.86% |
| 1243.3 | Yellow | Noyori technology -Ketone hydrogenation | 8.13% |
| 1243.3 | Yellow | Noyori technology -Ketone hydrogenation | 8.13% |
| 1167.15 | Yellow | Noyori technology -Ketone hydrogenation | 9.11% |
| 1167.15 | Yellow | Noyori technology -Ketone hydrogenation | 9.11% |
| 1165.2 | Yellow | Noyori technology -Ketone hydrogenation | 8.70% |
| 1165.2 | Yellow | Noyori technology -Ketone hydrogenation | 8.70% |
| 1028.9 | Yellow | Noyori technology -Ketone hydrogenation | 9.82% |
| 1028.9 | Yellow | Noyori technology -Ketone hydrogenation | 9.82% |
| 1031.1 | Yellow | Noyori technology -Ketone hydrogenation | 8.97% |
| 1031.1 | Yellow | Noyori technology -Ketone hydrogenation | 8.97% |
| 1141.11 | Yellow | Noyori technology -Ketone hydrogenation | 8.86% |
| 1141.11 | Yellow | Noyori technology -Ketone hydrogenation | 8.86% |
| 1243.3 | Yellow | Noyori technology -Ketone hydrogenation | 8.13% |
| 1243.3 | Yellow | Noyori technology -Ketone hydrogenation | 8.13% |
| 1167.15 | Yellow | Noyori technology -Ketone hydrogenation | 9.11% |
| 1167.15 | Yellow | Noyori technology -Ketone hydrogenation | 9.11% |
| 1028.9 | Yellow | Noyori technology -Ketone hydrogenation | 9.82% |
| 1028.9 | Yellow | Noyori technology -Ketone hydrogenation | 9.82% |
| 1031.1 | Yellow | Noyori technology -Ketone hydrogenation | 8.97% |
| 1031.1 | Yellow | Noyori technology -Ketone hydrogenation | 8.97% |
| 636.21 | Orange Brown | Transfer Hydrogenation of Ketones and Imines | 15.88% |
| 636.21 | Orange Brown | Transfer Hydrogenation of Ketones and Imines | 15.88% |
| 560.1 | Orange Brown | Transfer Hydrogenation of Ketones and Imines | 18.00% |
| 560.1 | Orange Brown | Transfer Hydrogenation of Ketones and Imines | 18.00% |
| 622.18 | Orange Brown | Transfer Hydrogenation of Ketones and Imines | 16.20% |
| 622.18 | Orange Brown | Transfer Hydrogenation of Ketones and Imines | 16.20% |
| 546.1 | Orange Brown | Transfer Hydrogenation of Ketones and Imines | 18.49% |
| 546.1 | Orange Brown | Transfer Hydrogenation of Ketones and Imines | 18.49% |
| 538.11 | Orange Brown | Transfer Hydrogenation of Ketones and Imines | 18.77% |
| 538.11 | Orange Brown | Transfer Hydrogenation of Ketones and Imines | 18.77% |
| 620.17 | Orange Brown | Transfer Hydrogenation of Ketones and Imines | 16.29% |
| 620.17 | Orange Brown | Transfer Hydrogenation of Ketones and Imines | 16.29% |
| 644.64 | White | Catalyst, when combined with Rh, Ru and Ir prec. | |
| 644.64 | White | Catalyst, when combined with Rh, Ru and Ir prec. | |
| 756.85 | White | Catalyst, when combined with Rh, Ru and Ir prec. | |
| 756.85 | White | Catalyst, when combined with Rh, Ru and Ir prec. | |

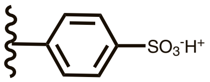
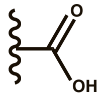
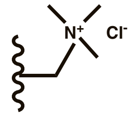
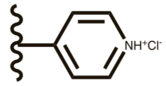
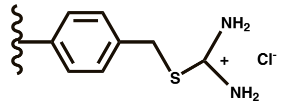
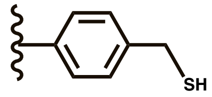
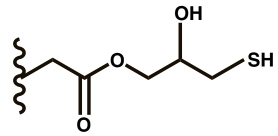
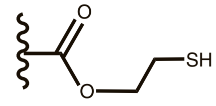
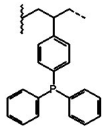
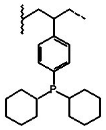
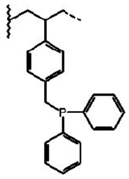
## CHIRAL HOMOGENOUS CATALYSTS – (CONTINUED)

| Compound | CAS Numbers | JM Name | Formula |
|---|---|---|---|
| (R)-Xyl-P-Phos Ru (acac)$_2$ | – | C1-352 | $C_{56}H_{64}N_2O_8P_2Ru$ |
| (S)-Xyl-P-Phos Ru (acac)$_2$ | – | C1-362 | $C_{56}H_{64}N_2O_8P_2Ru$ |
| [Rh cod (R)-PPhos]BF$_4$ | 573718-56-6 | C2-000 | $C_{46}H_{48}BF_4N_2O_4P_2Rh$ |
| [Rh cod (S)-PPhos]BF$_4$ | – | C2-010 | $C_{46}H_{48}BF_4N_2O_4P_2Rh$ |
| [Rh cod (R)-Binap]BF$_4$ | 120521-81-5 | C2-040 | $C_{52}H_{44}BF_4P_2Rh$ |
| [Rh cod (S)-Binap]BF$_4$ | 208118-82-5 | C2-060 | $C_{52}H_{44}BF_4P_2Rh$ |
| [Rh ((R)-Binap)$_2$] BF$_4$ | – | C7-040 | $C_{88}H_{64}BF_4P_4Rh$ |
| [Rh ((S)-Binap)$_2$] BF$_4$ | 98302-53-5 | C7-050 | $C_{88}H_{64}BF_4P_4Rh$ |
| [Rh cod DiPFc] BF$_4$ | 255064-36-9 | C2-900 | $C_{30}H_{48}BF_4P_2Rh$ |
| [Rh cod (rac)-Binap] BF$_4$ | 439801-50-0 | C2-905 | $C_{52}H_{44}BF_4P_2Rh$ |
| [Rh cod (PPh$_3$)$_2$] BF$_4$ | 32762-45-1 | C2-910 | $C_{44}H_{42}BF_4P_2Rh$ |
| (R)-Phanephos | 364732-88-7 | C4-005 | $C_{40}H_{34}P_2$ |
| (S)-Phanephos | 192463-40-4 | C4-025 | $C_{40}H_{34}P_2$ |
| (R)-An-Phanephos | 364732-86-5 | C4-008 | $C_{44}H_{42}O_4P_2$ |
| (S)-An-Phanephos | – | C4-028 | $C_{44}H_{42}O_4P_2$ |
| (R)-Xyl-Phanephos | 325168-89-6 | C4-007 | $C_{48}H_{50}P_2$ |
| (S)-Xyl-Phanephos | 325168-88-5 | C4-027 | $C_{48}H_{50}P_2$ |
| [Rh cod (R)-Phanephos]BF$_4$ | 849950-56-7 | C2-020 | $C_{48}H_{46}BF_4P_2Rh$ |
| [Rh cod (S)-Phanephos]BF$_4$ | 723343-30-4 | C2-030 | $C_{48}H_{46}BF_4P2Rh$ |
| [Rh cod (R)-Phanephos] O$_3$SCF$_3$ | 192464-14-5 | C2-420 | $C_{49}H_{46}F_3O_3P_2RhS$ |
| [Rh cod (S)-Phanephos] O$_3$SCF$_3$ | 200808-74-8 | C2-430 | $C_{49}H_{46}F_3O_3P_2RhS$ |
| [Rh cod (R)-Xyl-Phanephos]BF$_4$ | 880257-53-4 | C2-022 | $C_{56}H_{62}BF_4P_2Rh$ |
| [Rh cod (S)-Xyl-Phanephos]BF$_4$ | 880136-41-4 | C2-032 | $C_{56}H_{62}BF_4P_2Rh$ |
| [Rh cod (R)-AnPhanephos]BF$_4$ | 1038932-68-1 | C2-023 | $C_{52}H_{54}O_4BF_4P_2Rh$ |
| [Rh cod (S)-AnPhanephos]BF$_4$ | – | C2-033 | $C_{52}H_{54}O_4BF_4P_2Rh$ |
| (R)-[Rh cod TCFP]BF$_4$ | 705945-70-6 | C2-801 | $C_{22}H_{44}BF_4P_2Rh$ |
| (S)-[Rh cod TCFP]BF$_4$ | 705945-68-2 | C2-802 | $C_{22}H_{44}BF_4P_2Rh$ |
| (R)-Me-Bophoz | 406680-94-2 | C4-040 | $C_{37}H_{35}Fe\ NP_2$ |
| (S)-Me-Bophoz | 406681-09-2 | C4-060 | $C_{37}H_{35}Fe\ NP_2$ |
| (R)-H8-BinamP | 208248-67-3 | C4-080 | $C_{44}H_{42}N_2P_2$ |
| (S)-H8-BinamP | 229177-79-1 | C4-100 | $C_{44}H_{42}N_2P_2$ |
| (R)-BinamP | 74974-14-4 | C4-120 | $C_{44}H_{34}N_2P_2$ |
| (S)-BinamP | 74974-15-5 | C4-140 | $C_{44}H_{34}N_2P_2$ |
| (Ra,Sc)-(1-Nph)-Quinaphos | 282715-27-9 | C4-200 | $C_{51}H_{35}NO_2P_2$ |
| (Sa,Rc)-(1-Nph)-Quinaphos | 282713-37-5 | C4-220 | $C_{51}H_{35}NO_2P_2$ |

## CHIRAL HOMOGENOUS CATALYSTS – (CONTINUED)

| Mol Wt | Color (Solid) | Selected Applications (prec. = precursor) | Metal Content |
|---|---|---|---|
| 1056.13 | Yellow | Unsaturated acid & functionalised ketone hydrog. | 9.57% |
| 1056.13 | Yellow | Unsaturated acid & functionalised ketone hydrog. | 9.57% |
| 944.54 | Yellow Orange | Hydrogenation of alkenes | 10.89% |
| 944.54 | Yellow Orange | Hydrogenation of alkenes | 10.89% |
| 920.56 | Yellow Orange | Hydrogenation of alkenes | 11.18% |
| 920.56 | Yellow Orange | Hydrogenation of alkenes | 11.18% |
| 1435.05 | Red Solid | Allylic Isomerisation | 7.17% |
| 1435.05 | Red Solid | Allylic Isomerisation | 7.17% |
| 716.22 | Yellow Orange | Hydrogenation of alkenes and ketones | 14.37% |
| 920.56 | Yellow Orange | Hydrogenation of alkenes | 11.18% |
| 822.46 | Yellow Orange | Hydrogenation of alkenes | 12.51% |
| 576.65 | White | Catalyst, when combined with Rh, Ru and Ir prec | |
| 576.65 | White | Catalyst, when combined with Rh, Ru and Ir prec. | |
| 696.75 | White | Catalyst, when combined with Rh, Ru and Ir prec. | |
| 696.75 | White | Catalyst, when combined with Rh, Ru and Ir prec. | |
| 688.87 | White | Catalyst, when combined with Rh, Ru and Ir prec. | |
| 688.87 | White | Catalyst, when combined with Rh, Ru and Ir prec. | |
| 874.54 | Yellow Orange | Hydrogenation of alkenes and ketones | 11.77% |
| 874.54 | Yellow Orange | Hydrogenation of alkenes and ketones | 11.77% |
| 936.8 | Yellow Orange | Hydrogenation of alkenes and ketones | 10.98% |
| 936.8 | Yellow Orange | Hydrogenation of alkenes and ketones | 10.98% |
| 896.75 | Yellow Orange | Hydrogenation of alkenes and ketones | 11.47% |
| 896.75 | Yellow Orange | Hydrogenation of alkenes and ketones | 11.47% |
| 994.64 | Yellow Orange | Hydrogenation of alkenes and ketones | 10.35% |
| 994.64 | Yellow Orange | Hydrogenation of alkenes and ketones | 10.35% |
| 560.24 | Yellow Orange | Hydrogenation of alkenes and ketones | 18.37% |
| 560.24 | Yellow Orange | Hydrogenation of alkenes and ketones | 18.37% |
| 611.5 | Yellow | Catalyst, when combined with Rh, Ru and Ir prec | |
| 611.5 | Yellow | Catalyst, when combined with Rh, Ru and Ir prec. | |
| 660.78 | White | Catalyst, when combined with Rh and Ir prec. | |
| 660.78 | White | Catalyst, when combined with Rh and Ir prec. | |
| 652.7 | White | Catalyst, when combined with Rh and Ir prec. | |
| 652.7 | White | Catalyst, when combined with Rh and Ir prec. | |
| 755.21 | White | Catalyst, when combined with Rh, Ru and Ir prec. | |
| 755.21 | White | Catalyst, when combined with Rh, Ru and Ir prec. | |

# 8. Table: Smopex® Metal Scavenging Products

| Trade name | Product description | Structure | Catalog No. |
|---|---|---|---|
| **SMOPEX®** | | | |
| Smopex-101 | Styrene sulfonic acid grafted polyolefin fibre |  | 125101 |
| Smopex-102* | Acrylic acid grafted polyolefin fibre |  | 125102 |
| Smopex-103 | Styryl trimethylamine grafted polyolefin fibre |  | 125103 |
| Smopex-105* | Vinyl pyridine grafted poleolefin fibre |  | 125105 |
| Smopex-110 | Styryl-based isothiouronium grafted polyolefin fibre |  | 125110 |
| Smopex-111* | Styryl thiol grafted polyolefin fibre |  | 125111 |
| Smopex-112 | Acrylate based "alpha"-hydroxyl thiol grafted polyolefin fibre |  | 125112 |
| Smopex-234* | Mercaptoethylacrylate grafted polyolefin fibre |  | 125234 |
| Smopex-301 | Triphenyl phosphine grafted polyolefin fibre |  | 125301 |
| Smopex-302 | Dicyclohexyl phenyl phosphine polyolefin fibre |  | 125302 |
| Smopex-303 | Diphenyl benzyl phosphine polyolefin fibre |  | 125303 |

Note: Typical dry content for Technical Grade Smopex is >20%.

*A Type II Drug Master File has been filed with the FDA. Details on development fibres are available on request.

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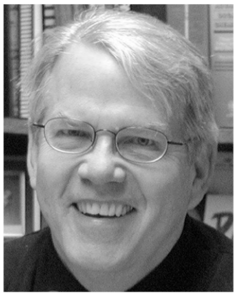
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